Accelerators For Medicine:

Achievements, Challenges, Opportunities

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History of medical applications of accelerators

1895 *Wilhelm Conrad Röntgen* (1845 – 1923) discovers the X-rays on 8th November at the University in Würzburg

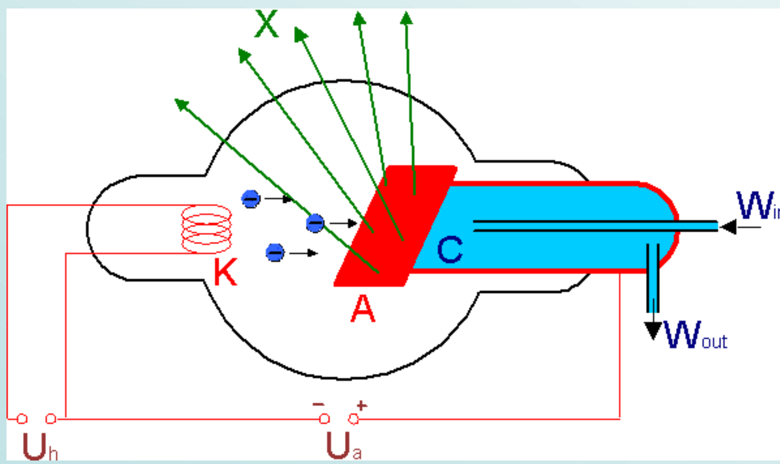
1896 On 23rd January Röntgen announced his discovery and demonstrated the new kind of radiation by a photograph of the hand of his colleague *Albert von Kolliker*

1897 First treatments of tissue with X-rays by *Leopold Freund* at University in Vienna

1901 Physics Nobel prize for W.C. Röntgen

Die durchleuchtete Hand von Bertha Röntgen 1895. Sie gilt als erste Röntgenaufnahme von einem Menschen.

Schematics of an X-ray tube – an "electrostatic accelerator"



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History:
High Voltage Therapy Of Cancer
Heidelberg, 1907

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History of medical applications of accelerators

1899 First X-ray treatment of carcinoma in Sweden by *Stenbeck* and *Sjögren*

1906 Vinzenz Czerny founded the "Institute for Experimental Cancer research" in Heidelberg – the first of its kind

1913/4 Invention of part- and full-rotation radiation instrumentation

1920´s Industrially manufactured X-ray apparatus; example from Reiniger-Gebbert & Schall AG (later: Siemens), Erlangen; 1922) with a high-voltage of 150 kV – without shielding!

1930 First linear accelerator principle invented by *Rolf Wideroe*

1949 *Newberry* developed first linear accelerator for therapy in England

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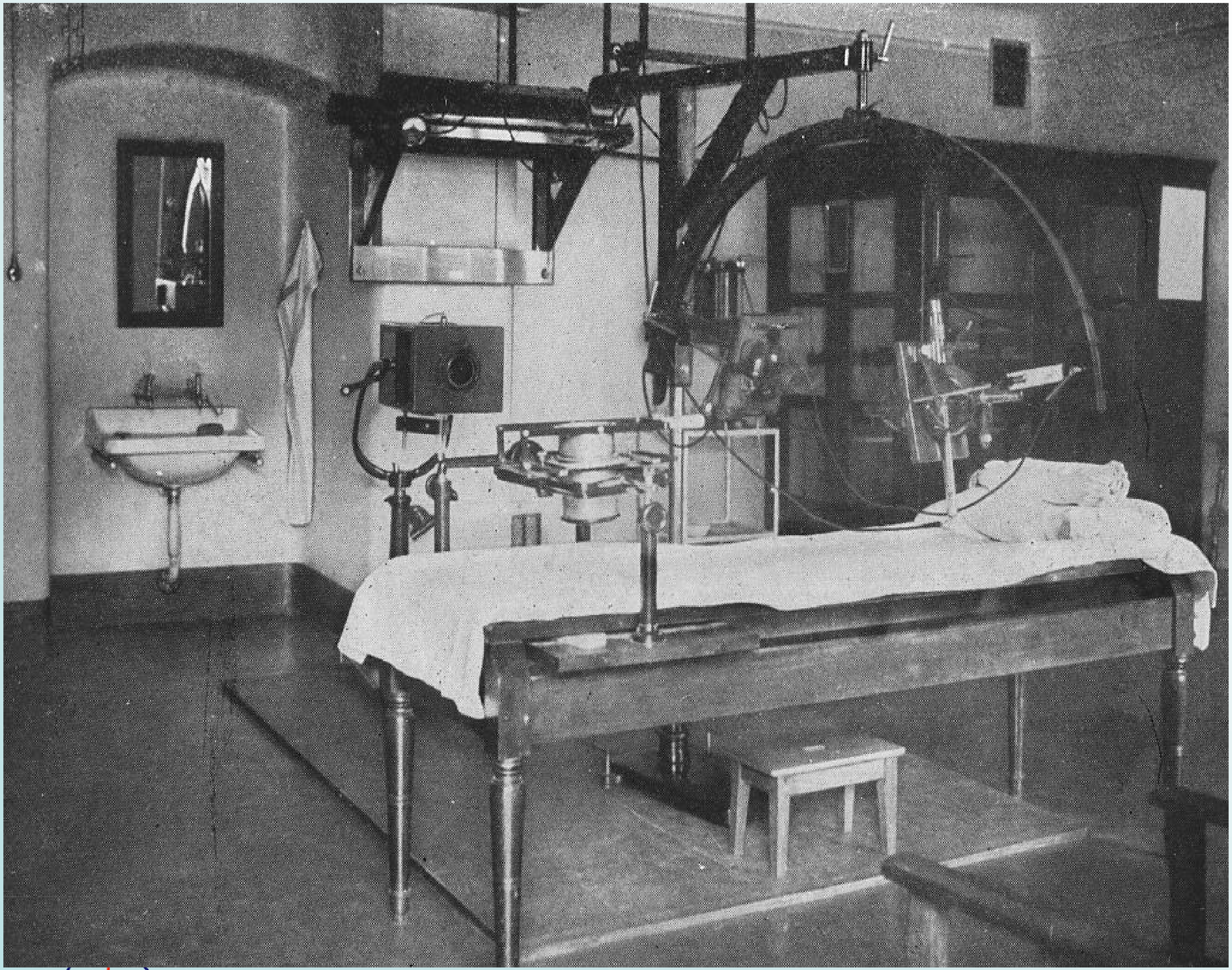
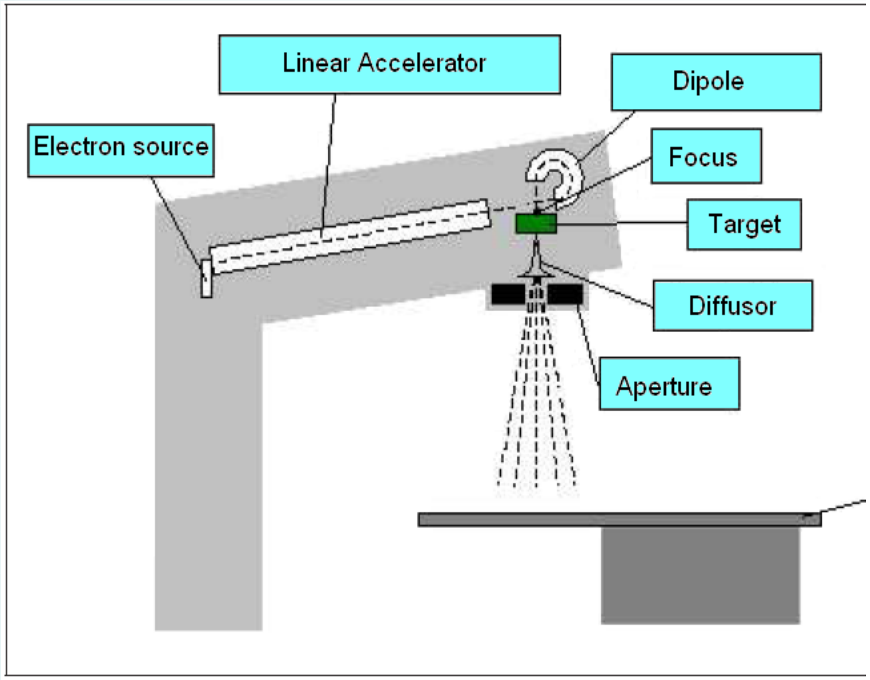
Radiation „Concentrator“, Heidelberg 1913



History of medical applications of accelerators

1950´s and later — Development of compact linear accelerators by Varian, Siemens, GE, Philipps and others with energies up to around 25 MeV (and above)

radiotherapy (Stanford linac)



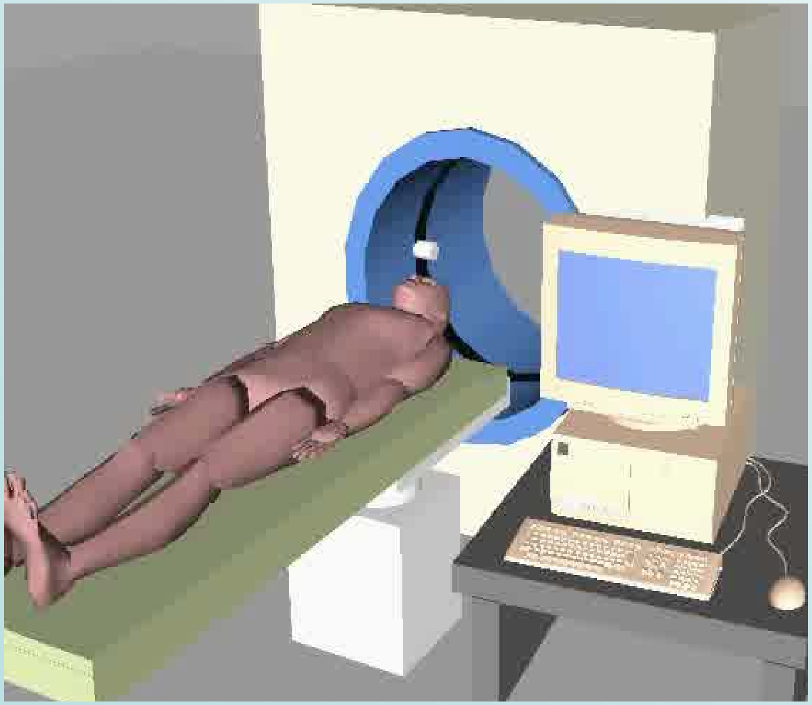
modern linac for therapy

today: 5-10 linacs per 1 million inhabitants

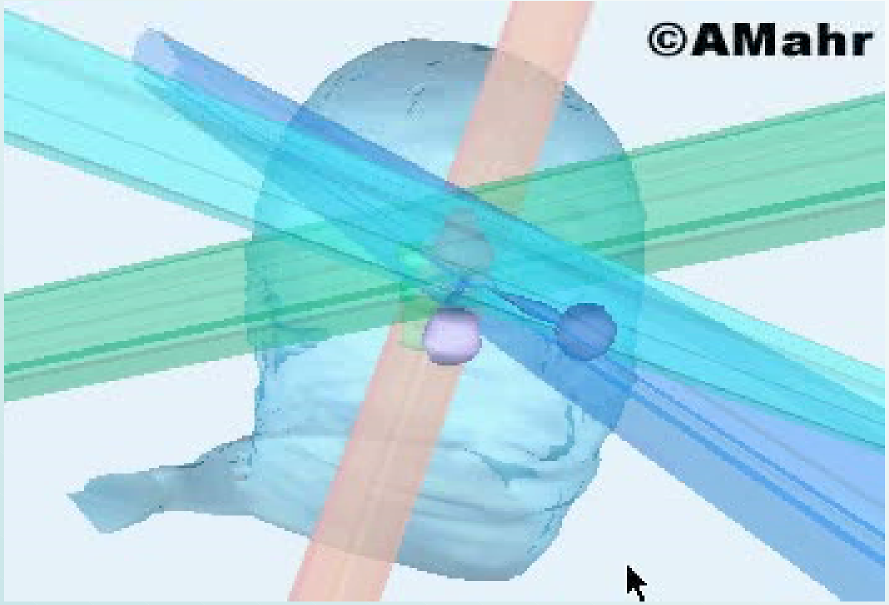
Treatment Planning:

Identify the target, model the patient, model the beam

1. model of the patient



2. model of the beam



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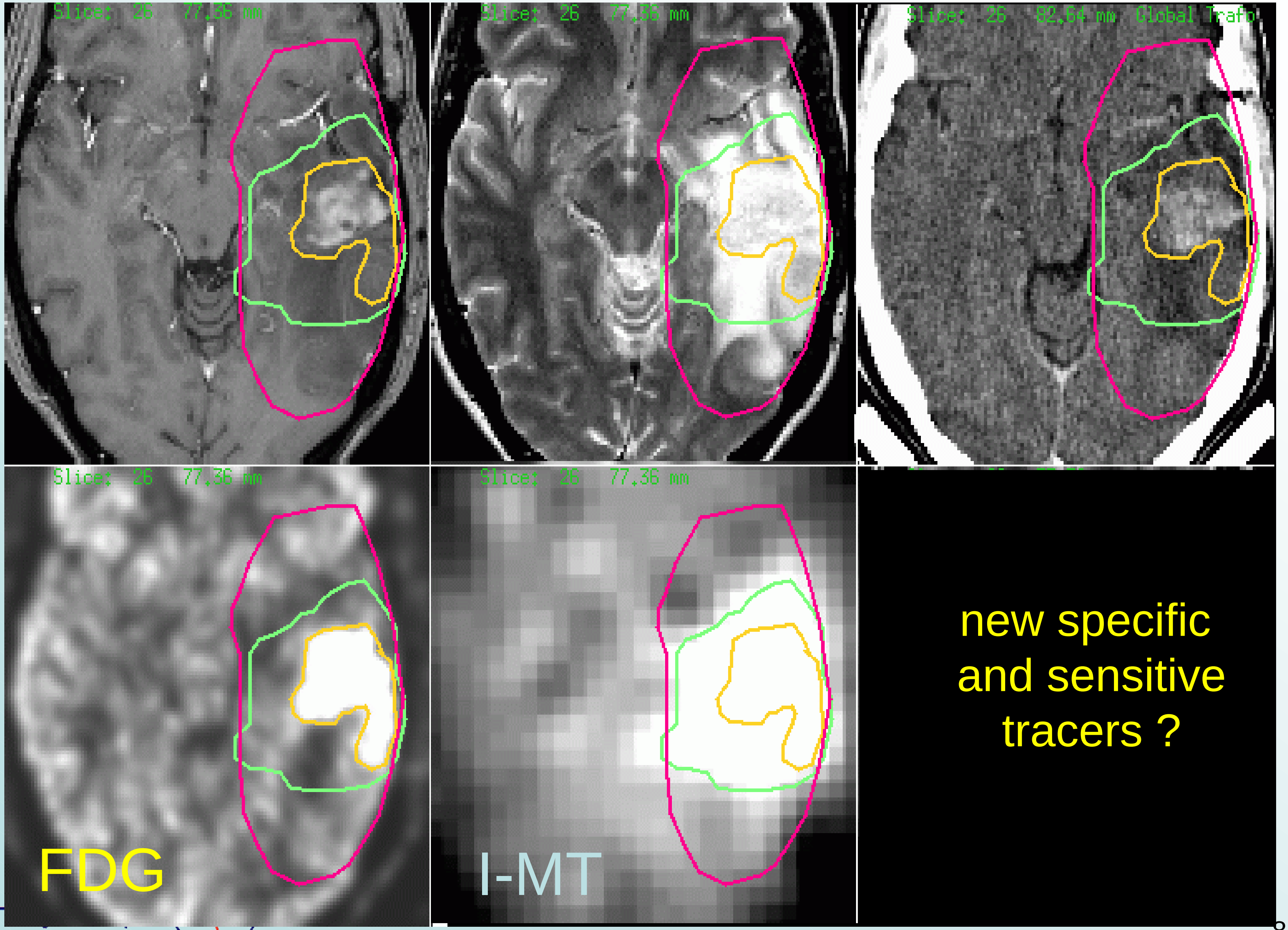
Target Defintion By Multi-Modal Imaging: Glioblastoma



PET Tracers In Oncology: Molecular Imaging

Metabolism

^{18}FDG

^{18}FECh

Amino acids

^{11}C-methionine

^{18}F-tyrosine

^{11}C-AIB

^{18}FET

Peptides

^{68}Ga-DOTATOC

Angiogenesis

^{18}F-Galacto-RGD

Perfusion

$H_2{}^{15}O$

Proliferation

^{11}C-thymidine

^{18}FLT

Hypoxia

^{18}F-MISO

Drugs

^{18}FU

many others experimentally

apoptoses, gen transfer etc.

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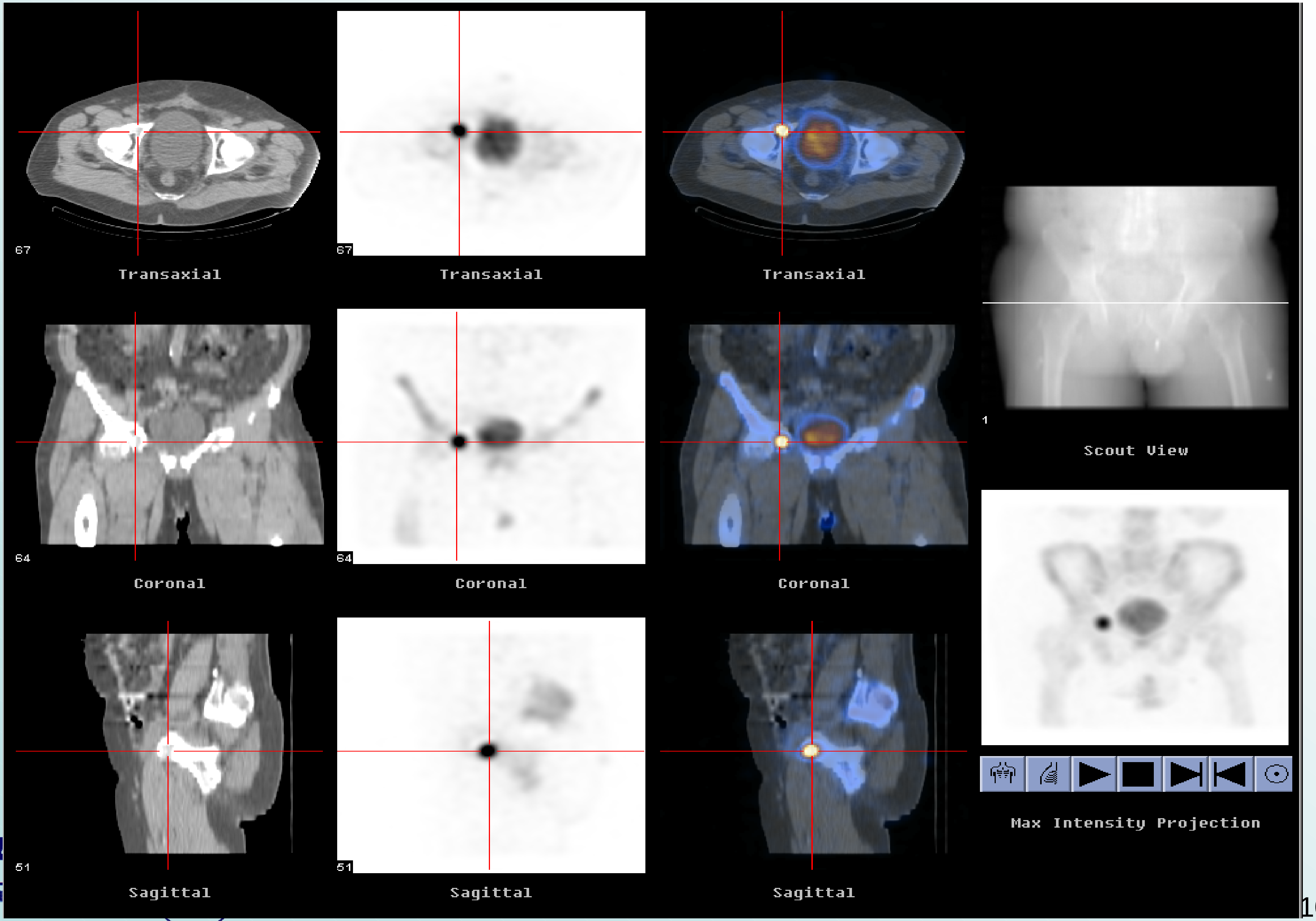
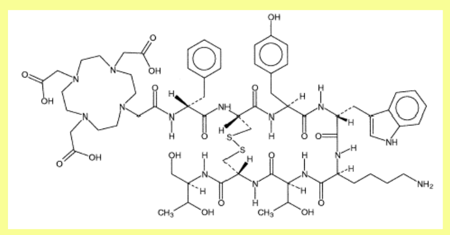
Sensitive Imaging Of Tumors: FECH PET In Recurrent Prostate Cancer (PSA 1,4)

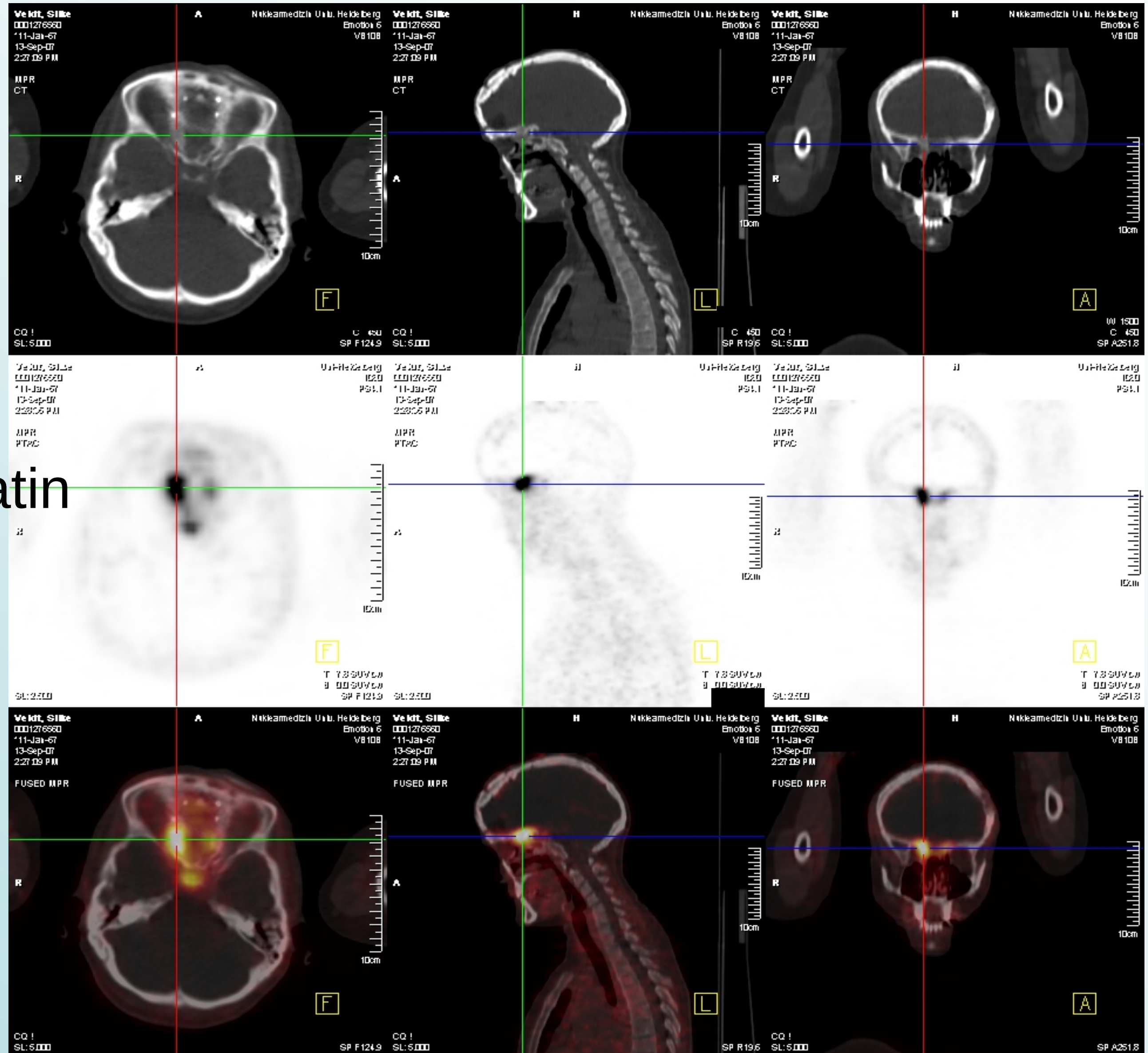


Imaging For RT Planning With DOTATOC: Recurrence Of Olfactorius Meningeoma

^{68}Ga-DOTATOC



Binds to somatostatin receptor type II



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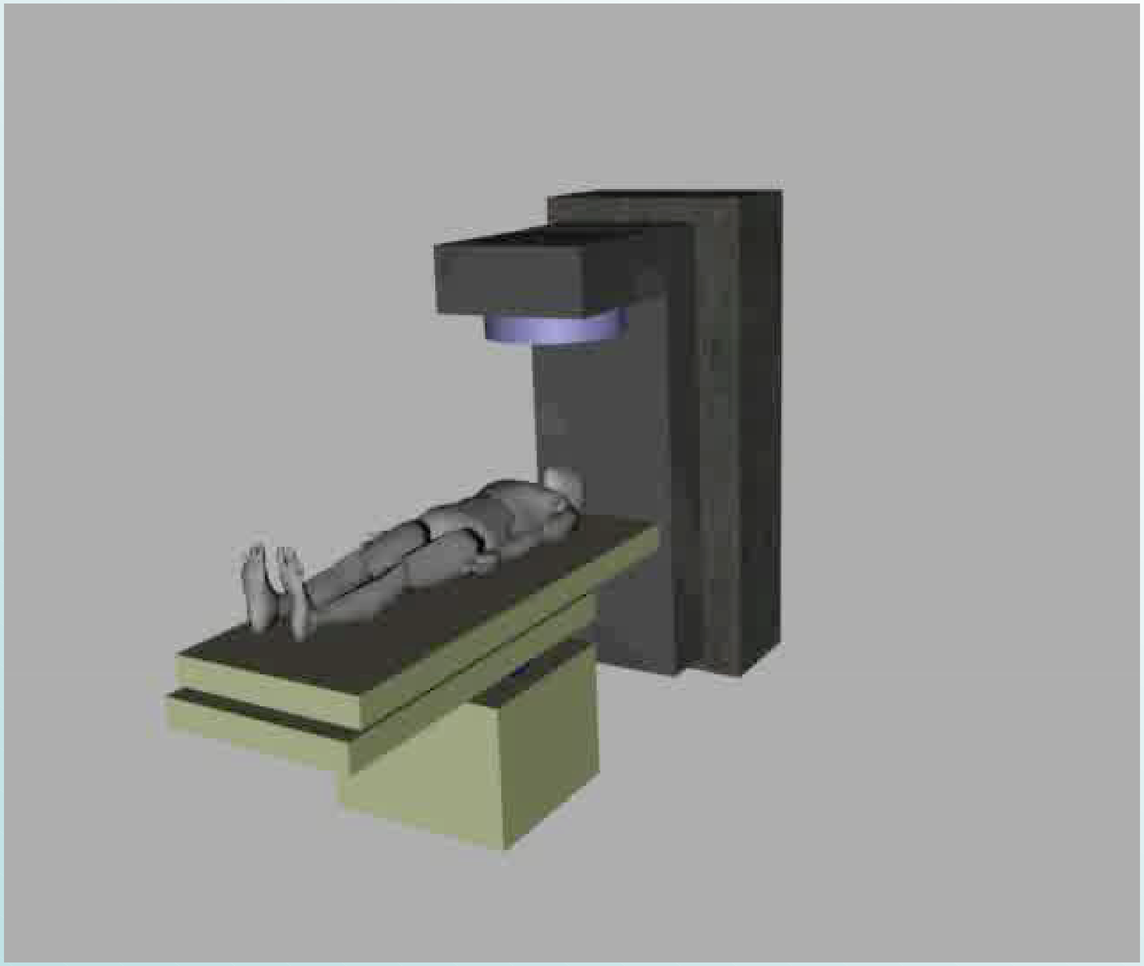
Intensity Modulated Radiotherapy (IMRT)



T. Bortfeld et al., DKFZ

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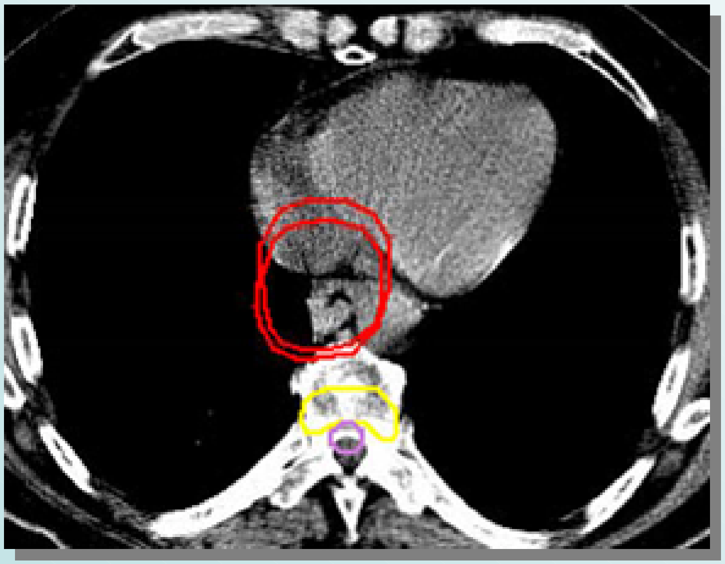
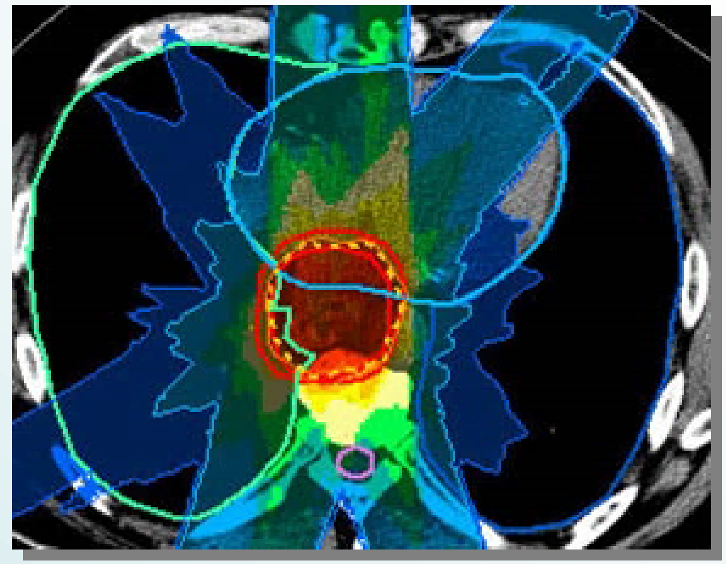
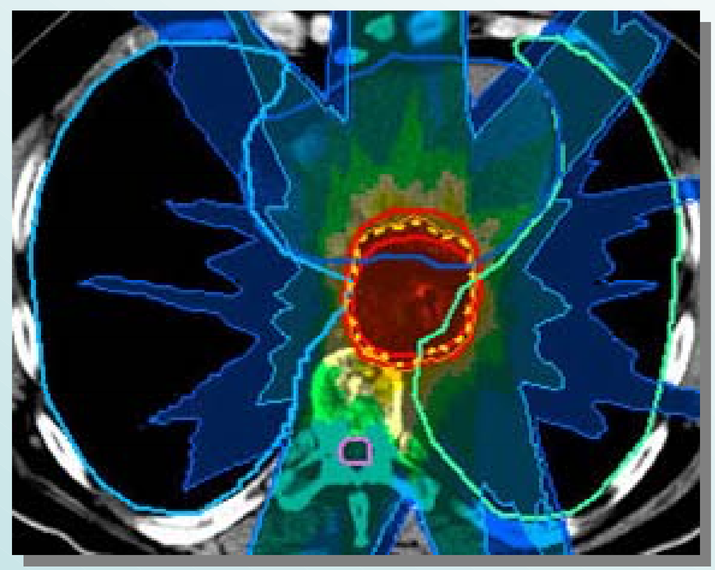
Esophageal Cancer:
Potential Variation Of The Target



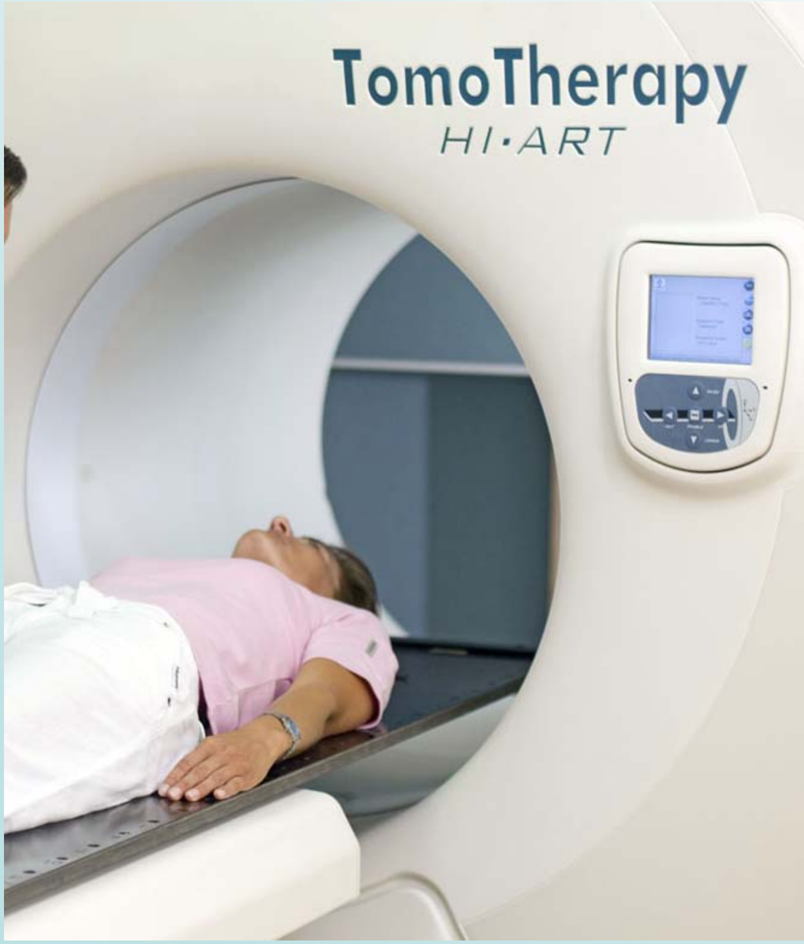
Var. 1:
9 days



Var. 2:
11 days



Integration Of Imaging And Treatment



- combination of CT-scanner

  and linear accelerator
- 85 cm Gantry-opening
- radiation volume

  diameter up to 40cm
  length up to 160cm
- 6 MV photons
- megavoltage CT (3MV)

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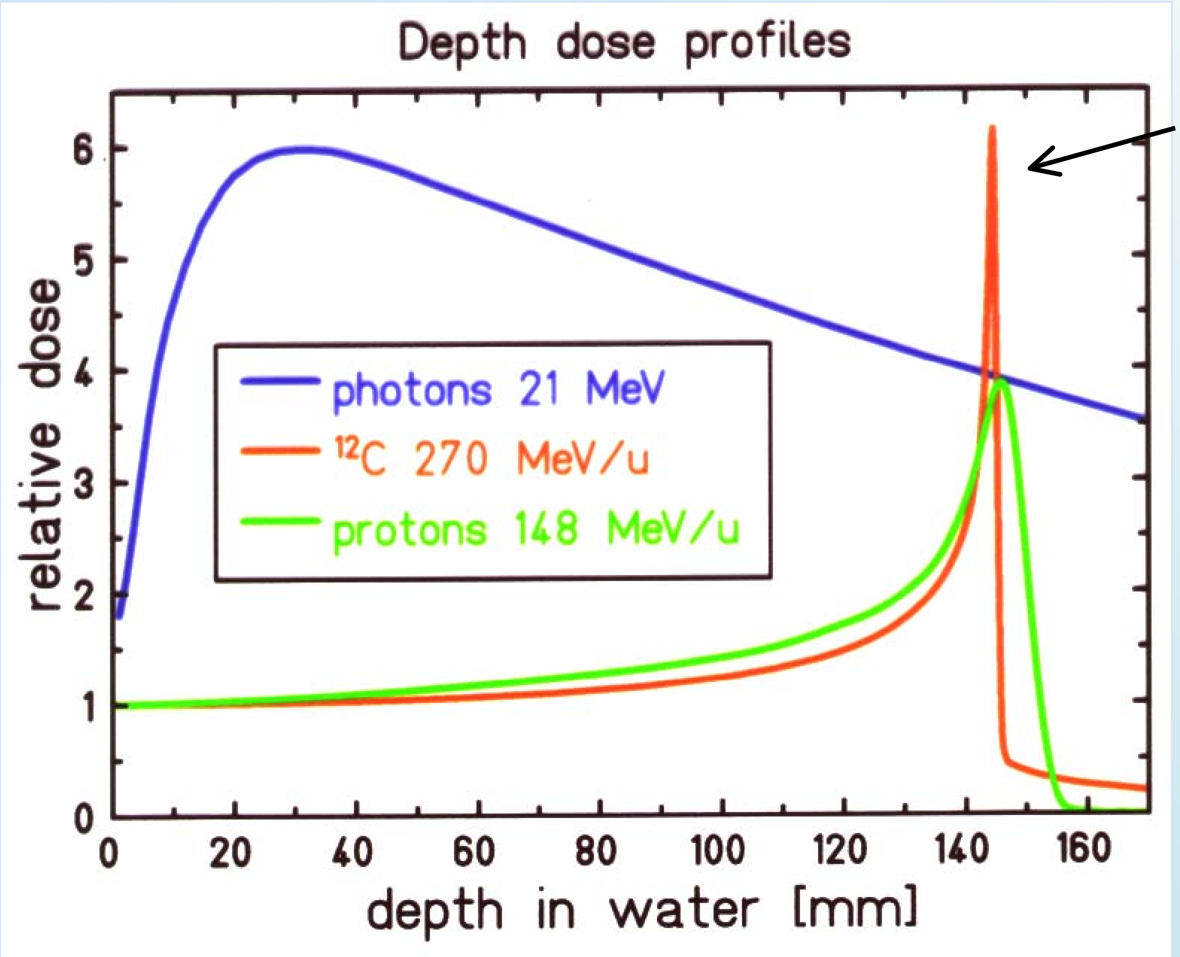
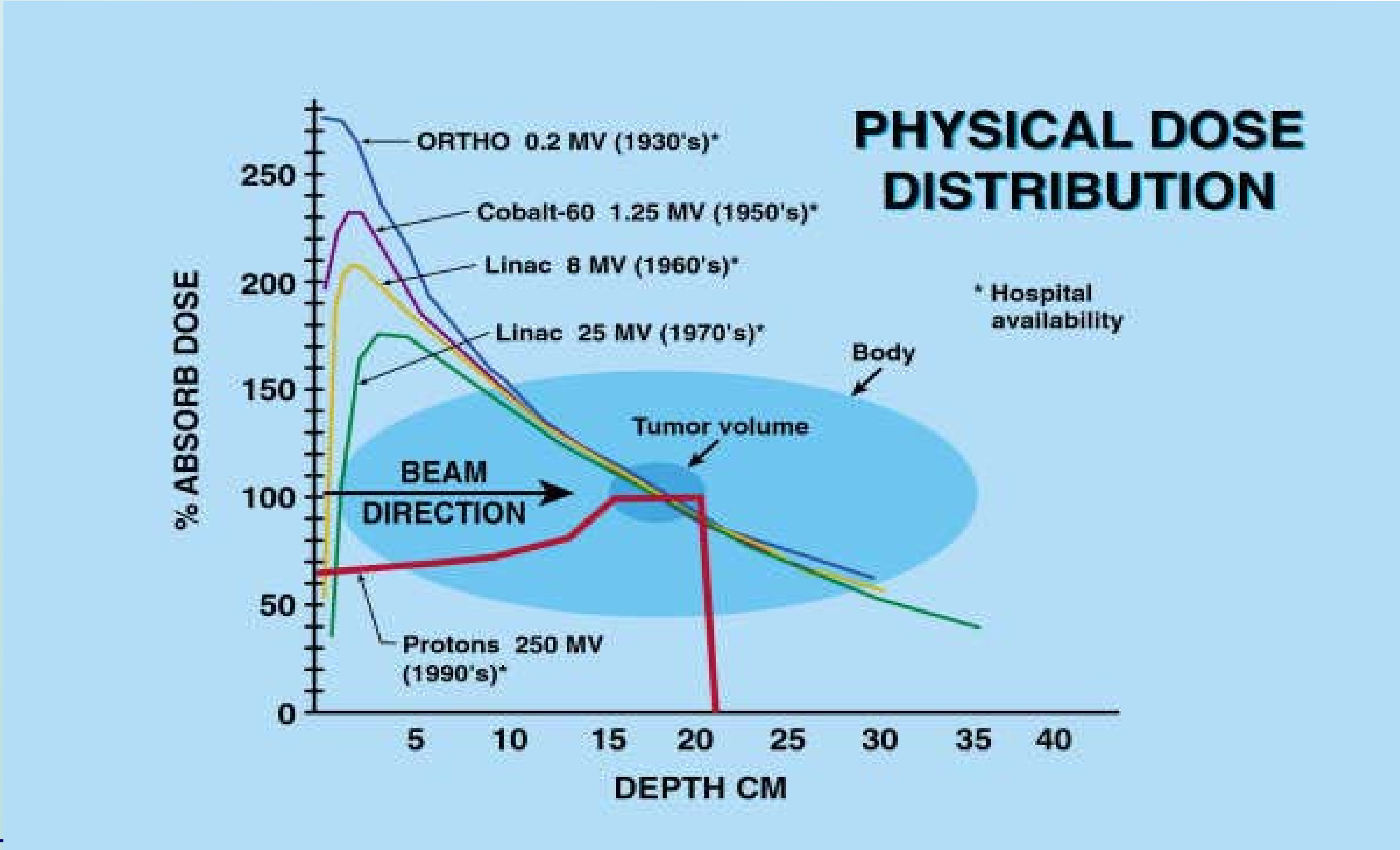
Charged Particle Beams Slow Down And Stop
X-rays keep going at the speed of light



„Bragg"-peak

Heavy Charged Particles In Radiotherapy
It's simply the physics!



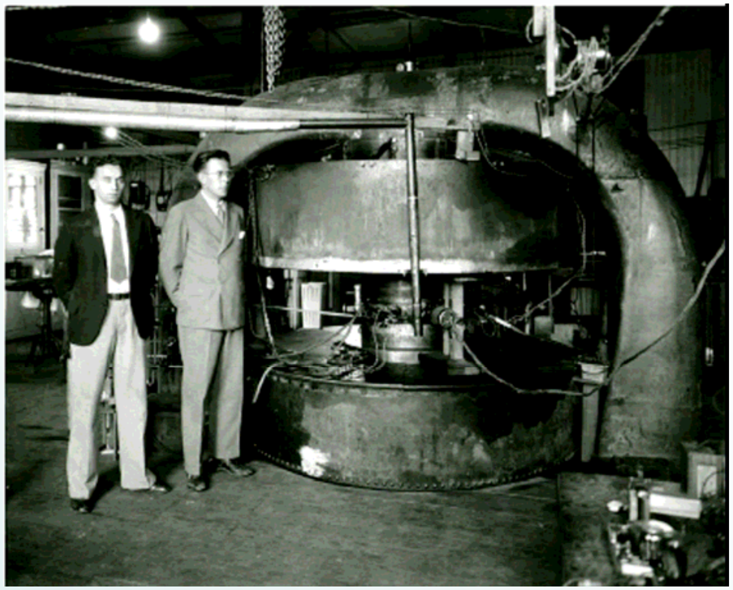
History of medical applications of accelerators

1929 Invention of cyclotron by *Ernest Lawrence*

1930´s Experimental neutron therapy

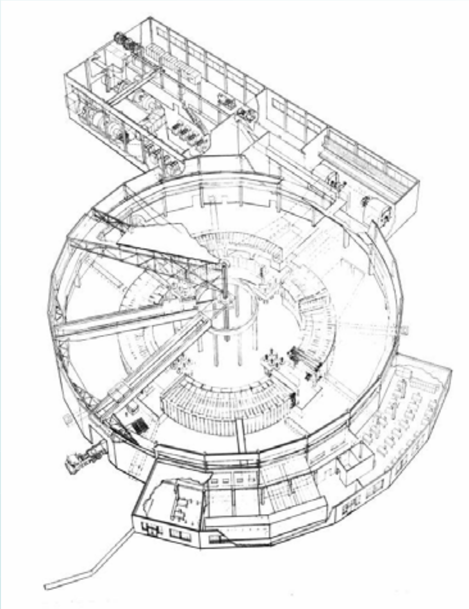
1946 R. R. Wilson proposed proton & ion therapy

1950's Proton therapy, LBL Berkeley (184" cyclotron)



1945 *Edwin Mattison McMillan* at University of California and *Vladimir Iosifovich Veksler* (Soviet Union) invented the synchrotron principle

1975 Begin of carbon therapy in Bevalac synchrotron (Berkeley)



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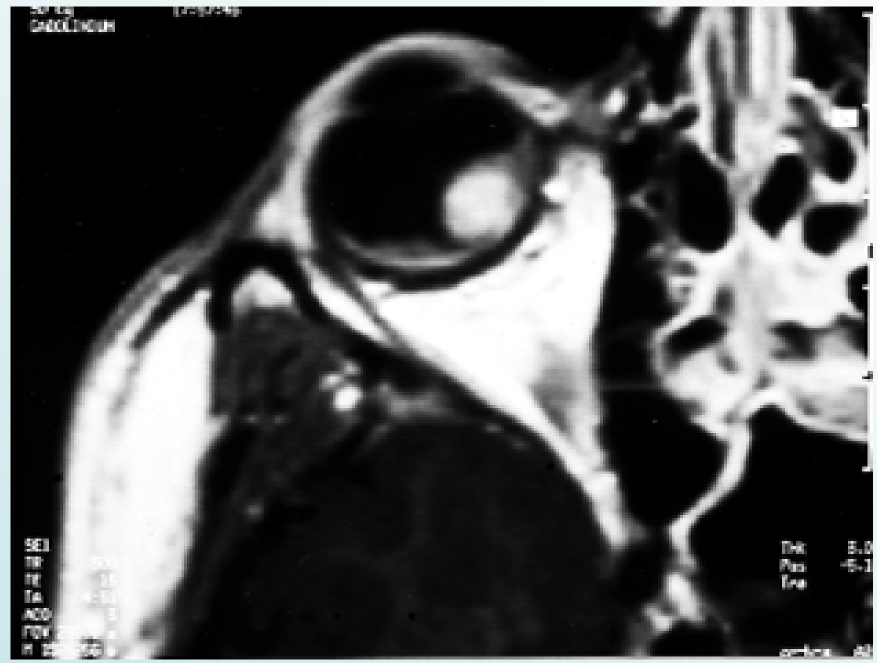
Harvard Cyclotron:
Patient Treatments 1974-2002

Treatment Of Occular Melanoma At The Harvard Cyclotron

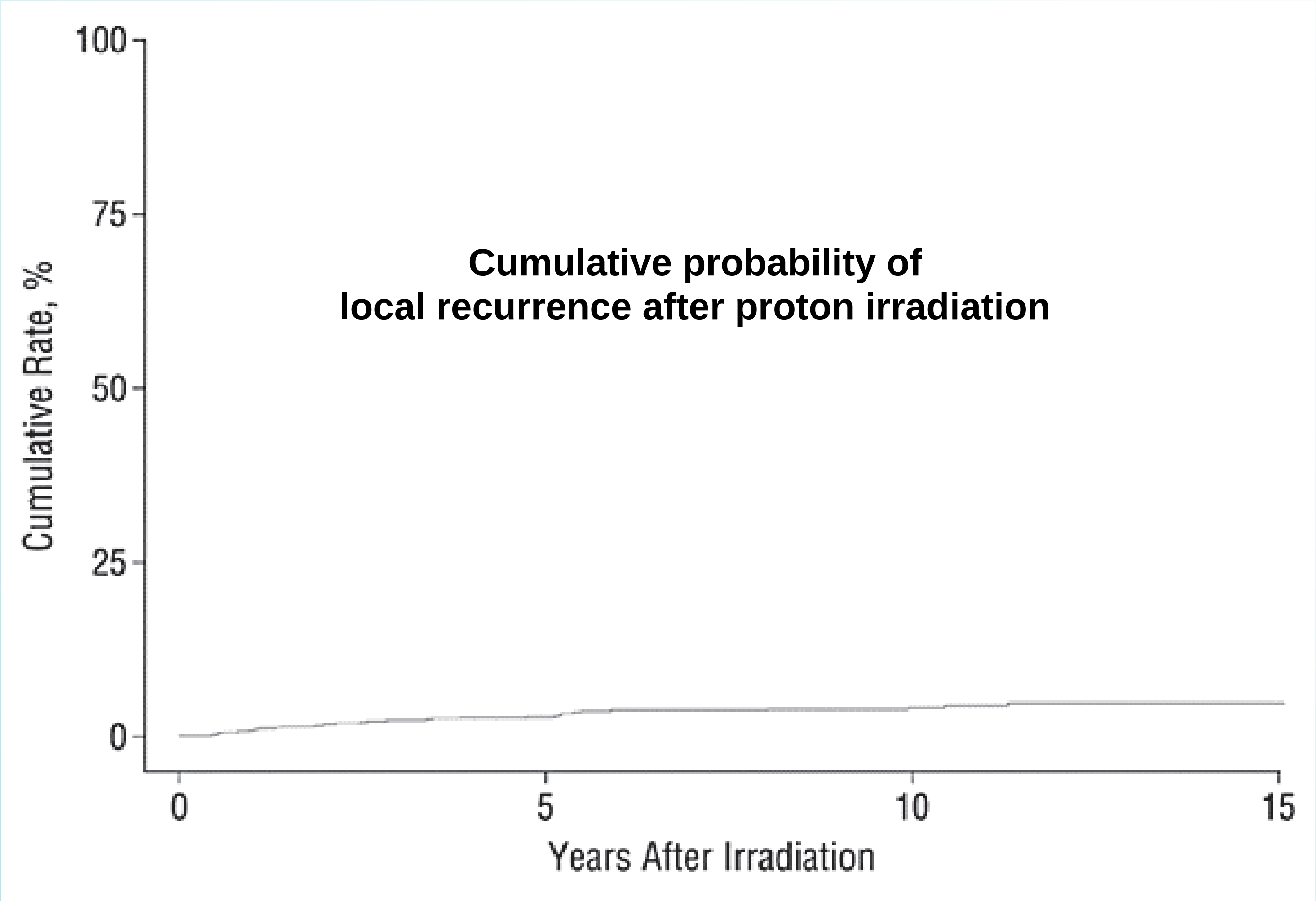
Occular Melanoma

Primary Symptom: reduced/disturbed vision



The MGH / MEEI Experience:

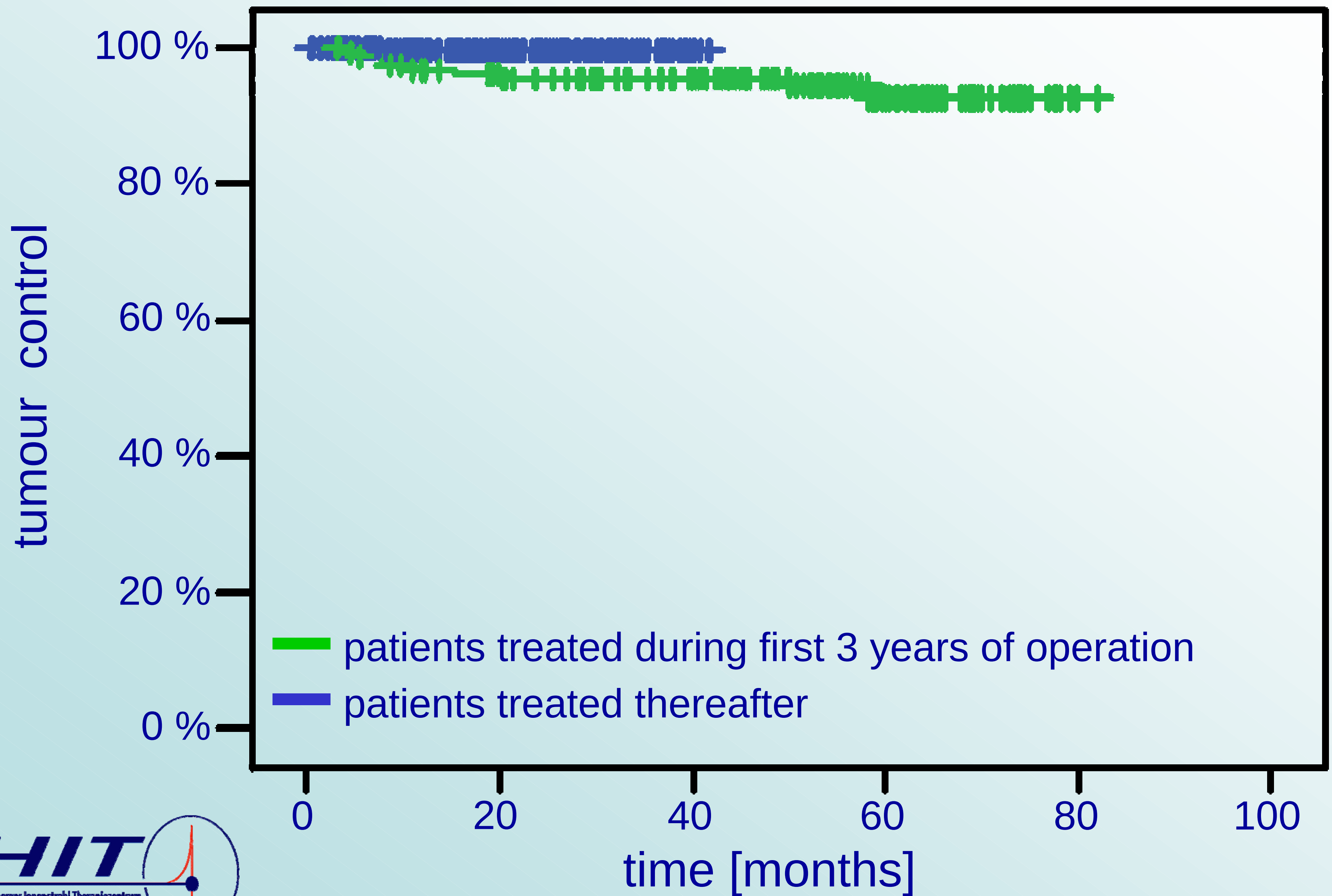
Gragoudas, E. et al. Arch Ophthalmol 2002;120:1665-1671.



ARCHIVES OF OPHTHALMOLOGY

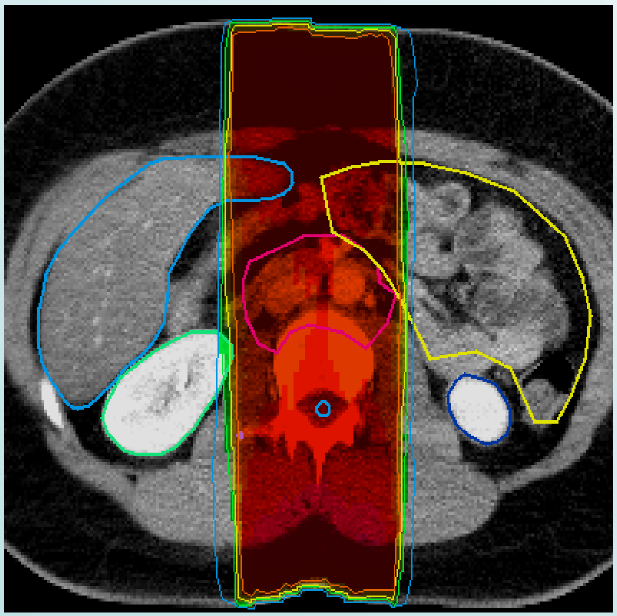
Ocular Melanoma Proton Therapy at Hahn-Meitner Institute

The „Learning Curve“ *(courtesy J. Heufelder)*

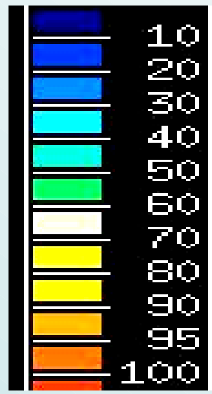


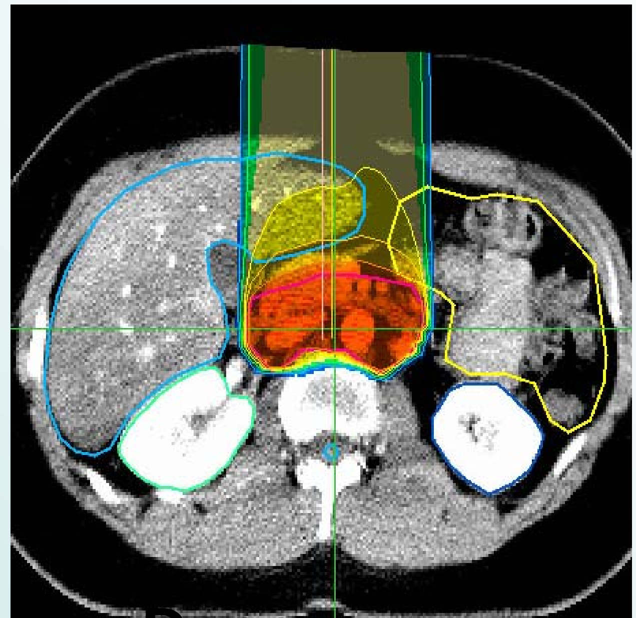
Potential Of Protons To Spare Uninvolved Structures
Radiotherapy Of Paraaortic Lymphnodes:
Challenge: Geometrical Changes During Treatment

Conventional Approach | **Particle Beams**



Dosis %





	Dose	
40 Gy	bone marrow	< 1 Gy
39 Gy	bowel	26 Gy
41 Gy	spinal cord	
	< 1 Gy	

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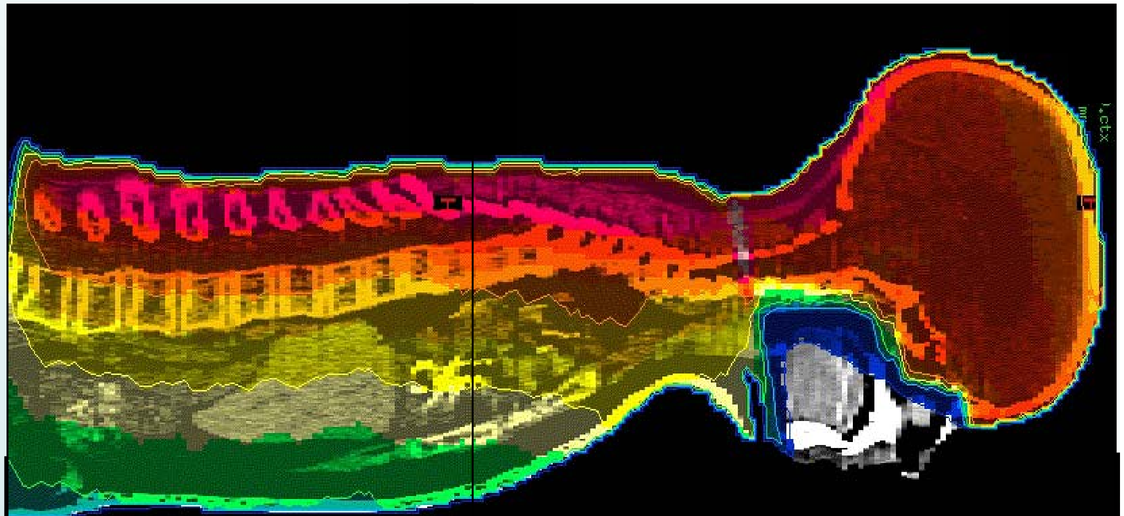
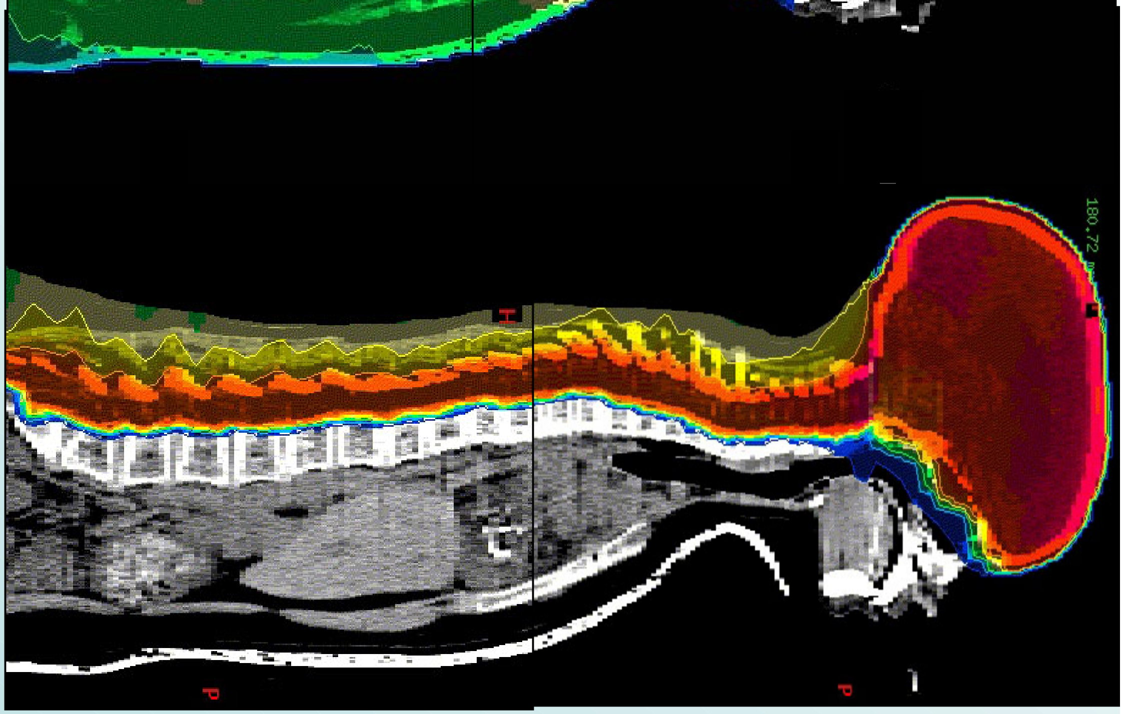
Craniospinal Radiotherapy For Medulloblastoma
charged particles can spare normal tissue

photons



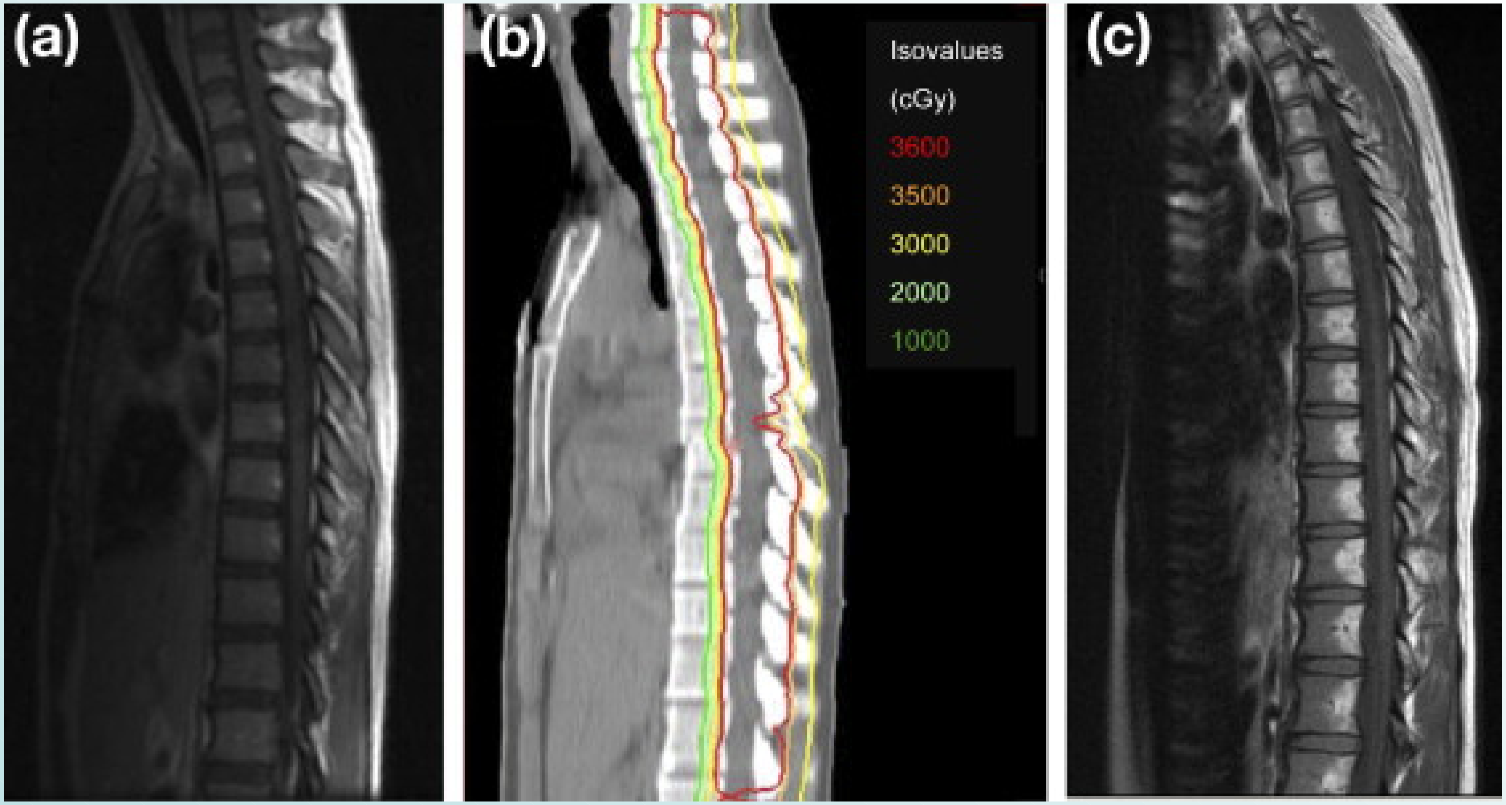
challenge:
size of the target !

particles



Craniospinal RT In 14 Year Old: Sparing Of Bone Marrow

Physiologic and Radiographic Evidence of the Distal Edge of the Proton Beam in Craniospinal Irradiation Krejcarek SC, Tarbell NJ, Yock TI et al. IJROBP 68(3):646-649, 2007



A 14-year-old girl with supratentorial primitive neuroectodermal tumor: craniospinal irradiation prescribed to the thecal sac and exiting nerve roots only. (a) T1-weighted magnetic resonance image 1 week before radiation treatment. (b) proton radiotherapy treatment plan. (c) T1-weighted MRI with hyperintense fatty changes in posterior aspect of vertebral bodies 1 month after PRT.

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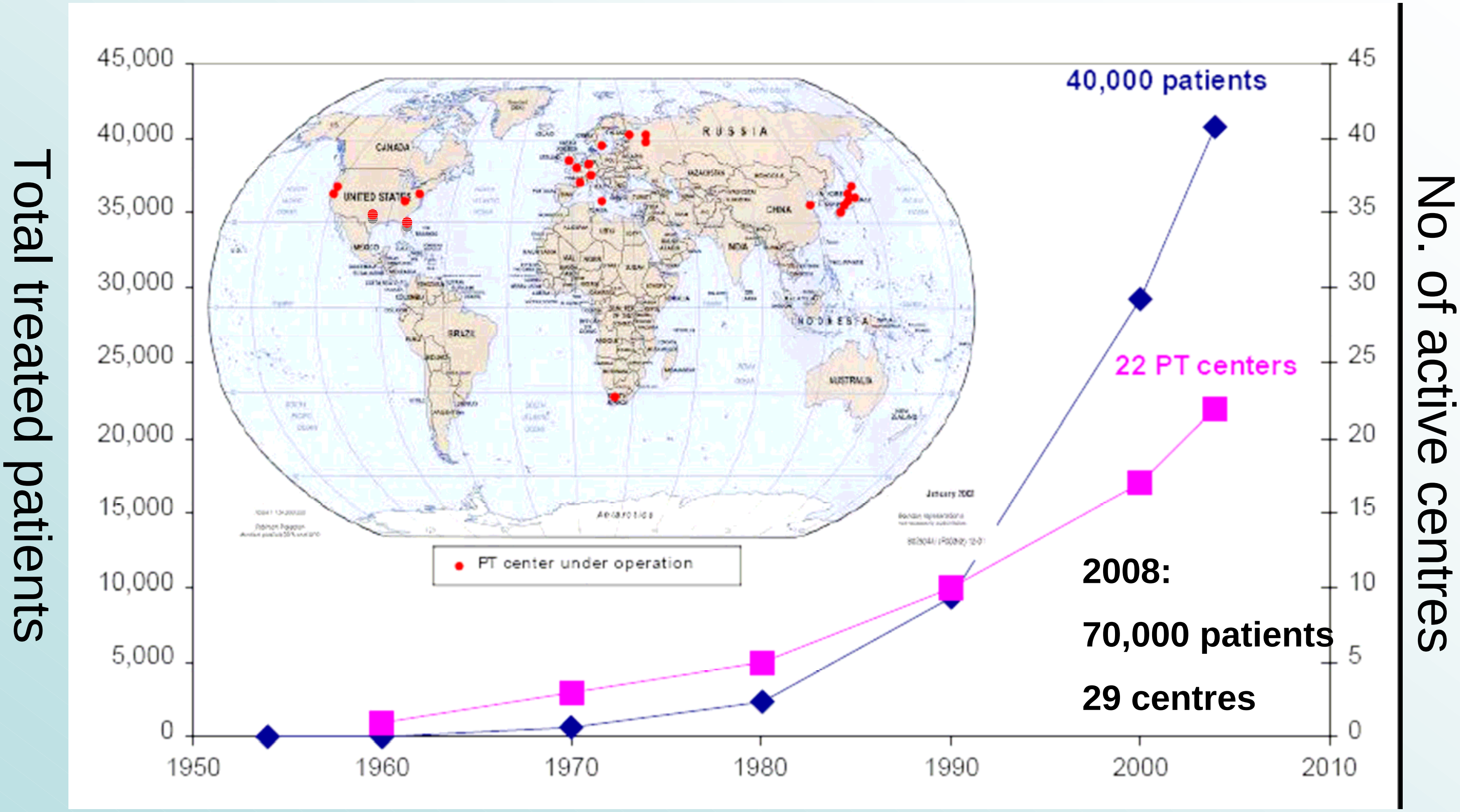
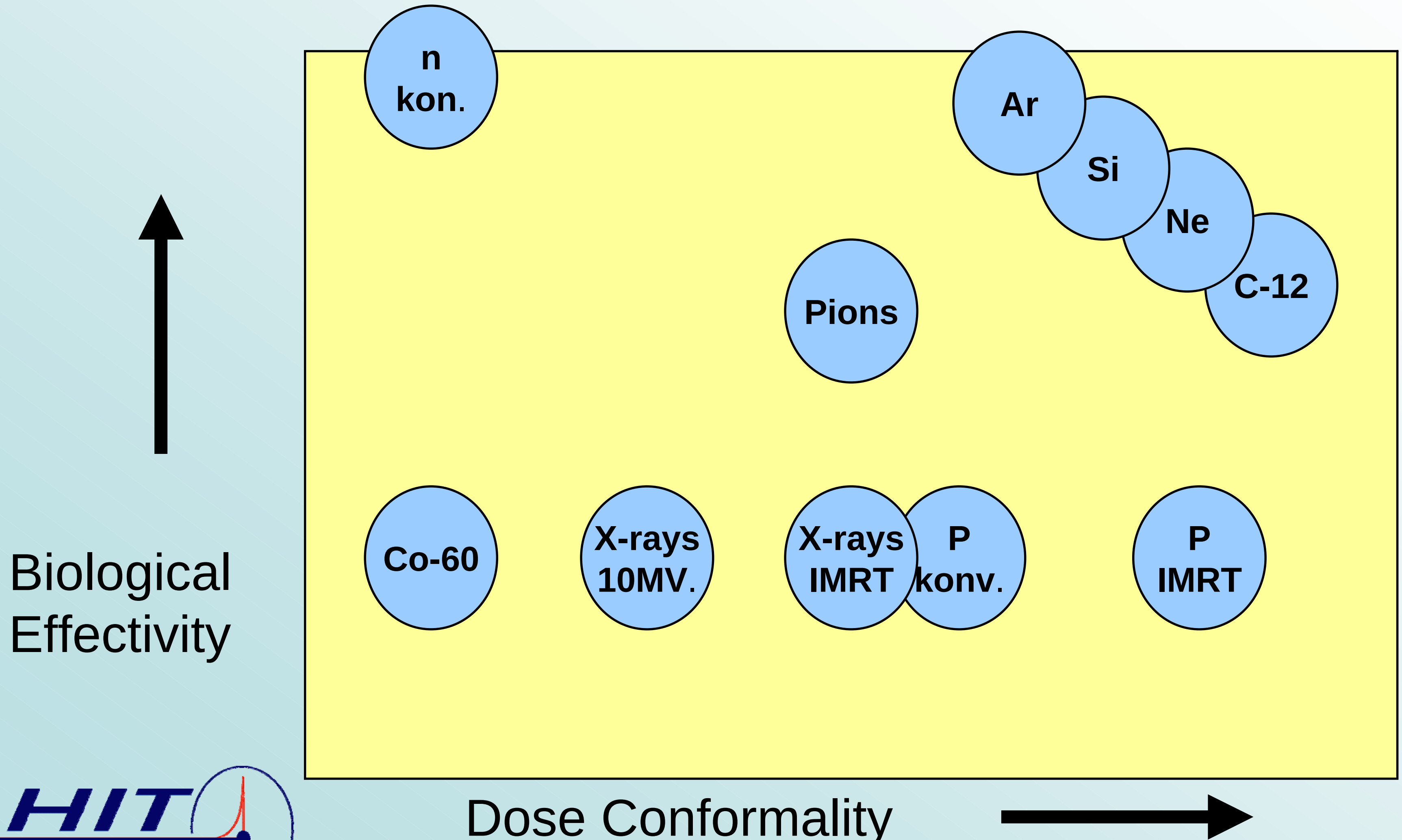
Particle Therapy Facilities - worldwide



PT centres: a rapidly growing market

Particles in Radiation Oncology

Comparison of Protons, Neutrons, Pions, Ions and Photons



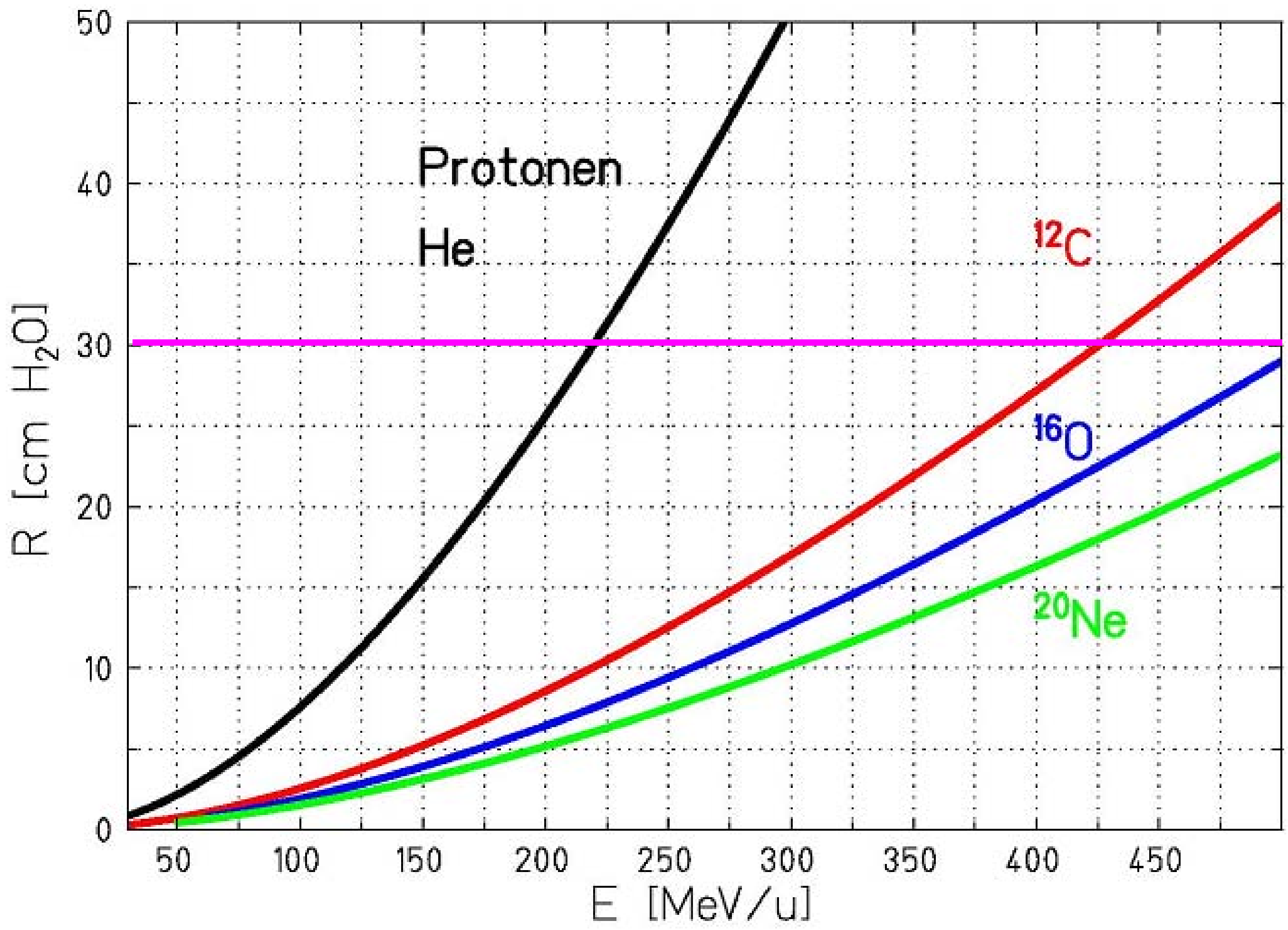
Implications on the beam energy

Range of different beams in water

30 cm range define the end energy for the accelerator design:

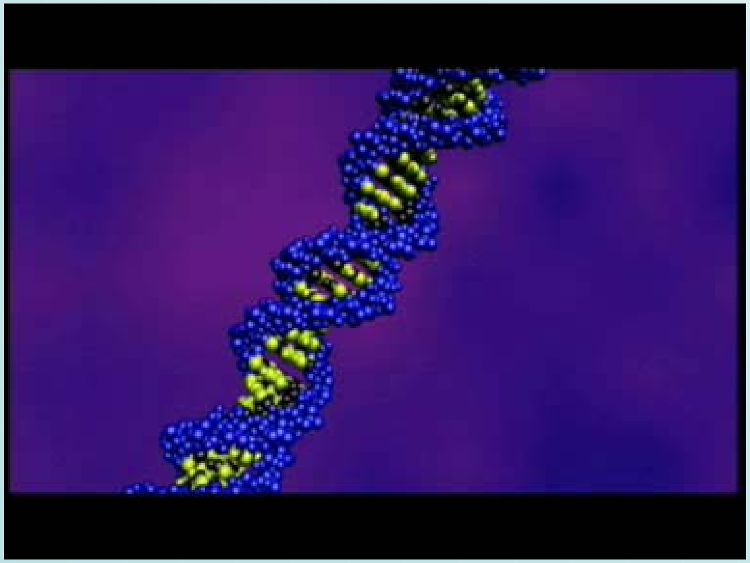
p → 220 MeV

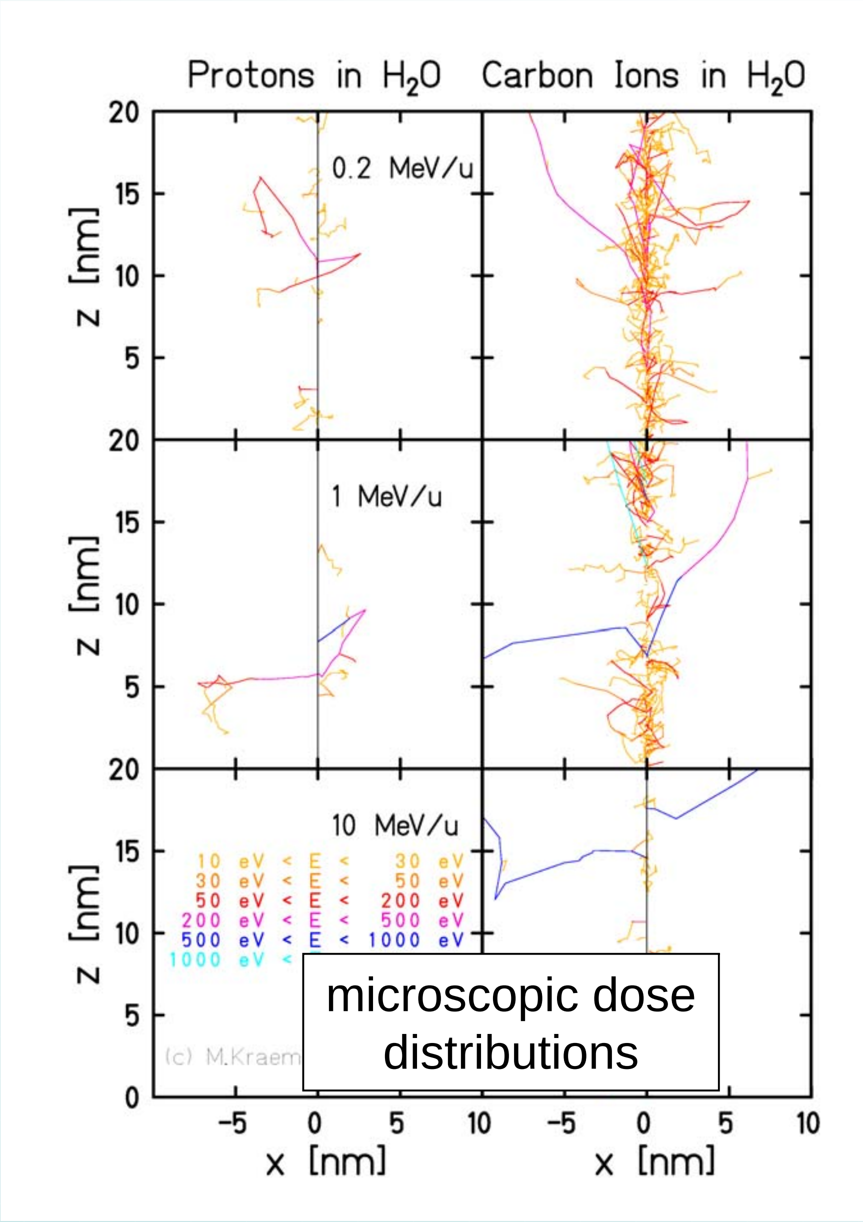
C → 430 MeV/u



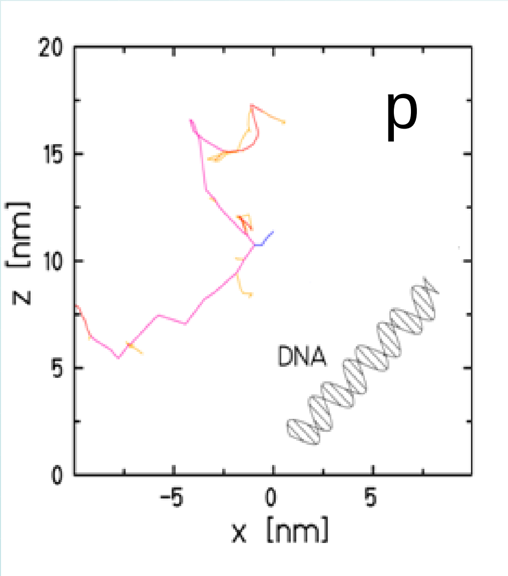
Physics and Biology of radiation therapy

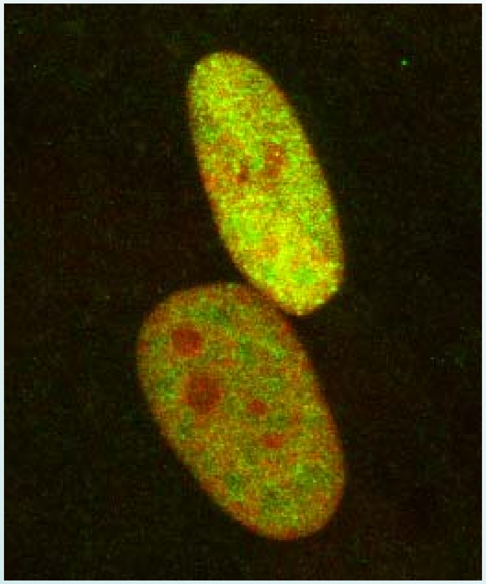
Basic effect of radiation on cells: energy loss in matter leads to defects in the DNA – double strand breaks of the DNA kills the cell. Tumor cells have less repair capabilities than normal cells.





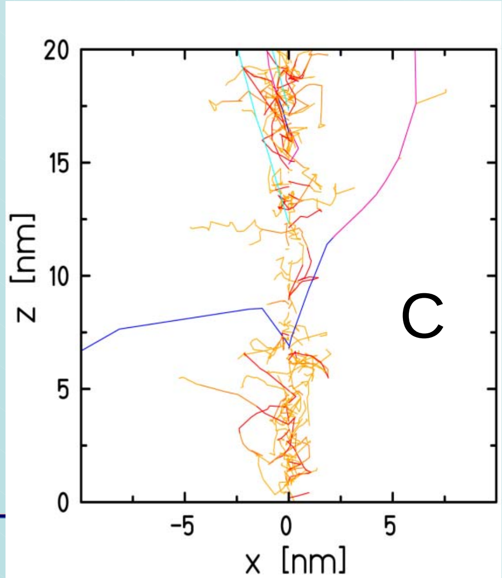
Physics and Biology of radiation therapy

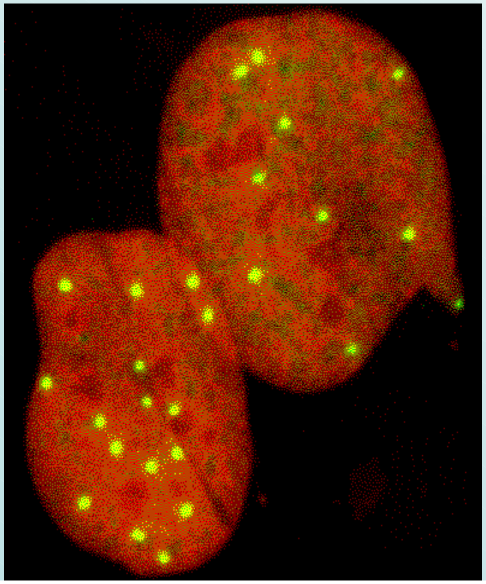




Low LET

Homogeneous deposition of dose





High LET

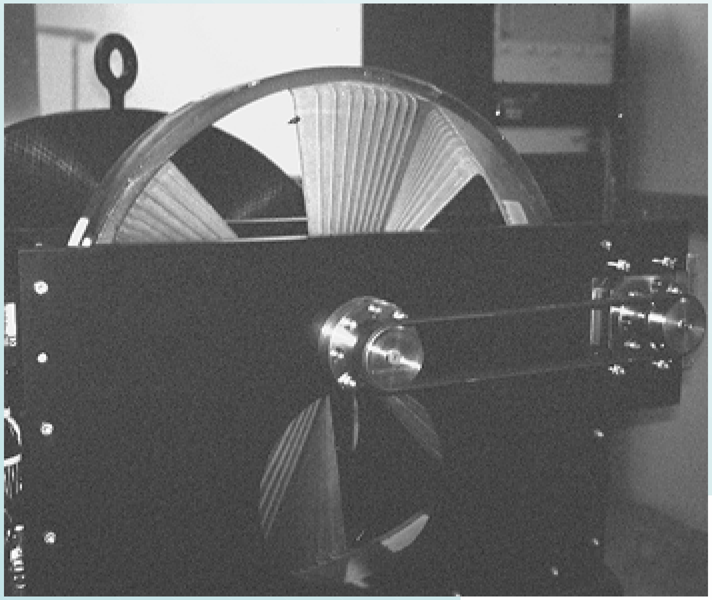
Local deposition of high doses

LET: Linear energy transfer

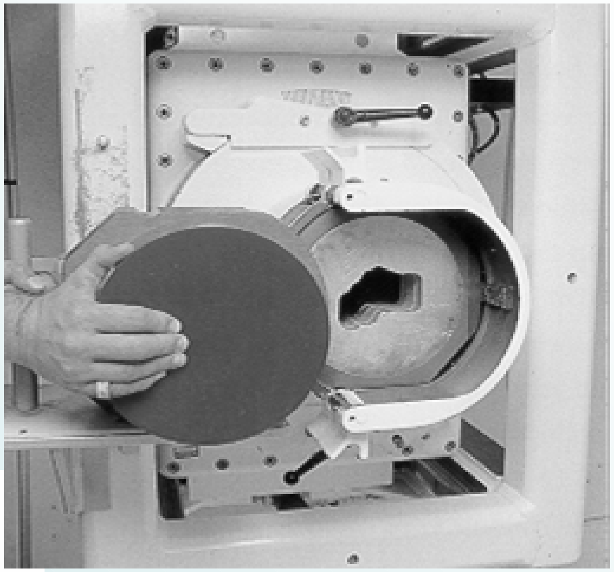
LBL, Berkeley, US Neon ion experience 1979-1998; 239 pts (Linstadt, 1991)

Tumor	# pts	Dose GyE (med.)	5y-LC	5y-DSS
Lung st. II-III	20	48-74 (63)	12 %	5 %
Esophagus	14	37-89 (68)	-	-
Stomach	9	45-60 (56)	37 %	11 %
Pancreas	64	30-71 (58)	6 % (3yrs)	1.5 % (OS)
Biliary tract	13	48-68 (60)	44 %	28 %
Prostate	12	70-79 (77)	75 %	90 %
Soft T. Sarcoma	12	37-80 (60)	56 %	56 %
Bone Sarcoma	19	50-76 (70)	59 %	45 %
Paran.sinus	12		69 %	69 %
Saliv. gland	18		61 %	59 %
Melanoma	6	48-80 (60)	-	-
Miscellaneous	40			

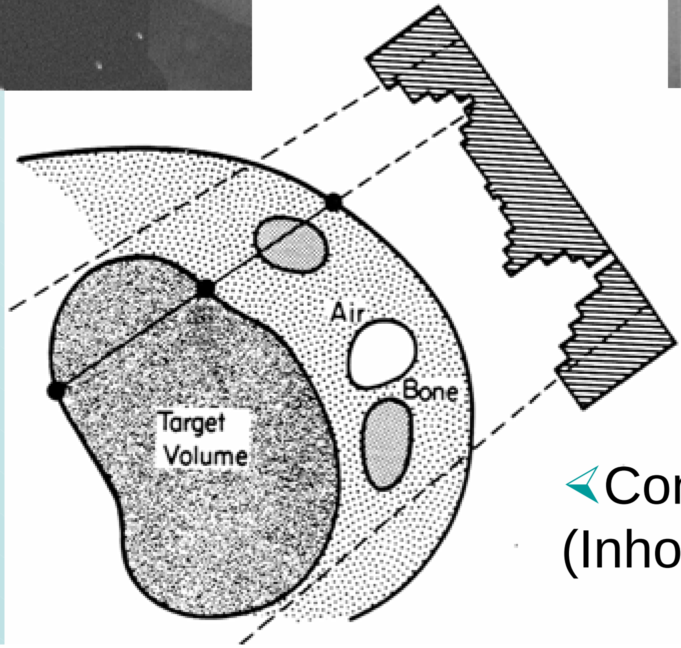
Conforming the Beam to the Target: Scattering Method



Modulator
(Thickness)



Collimator
(Shape)



Compensator
(Inhomogeneities)

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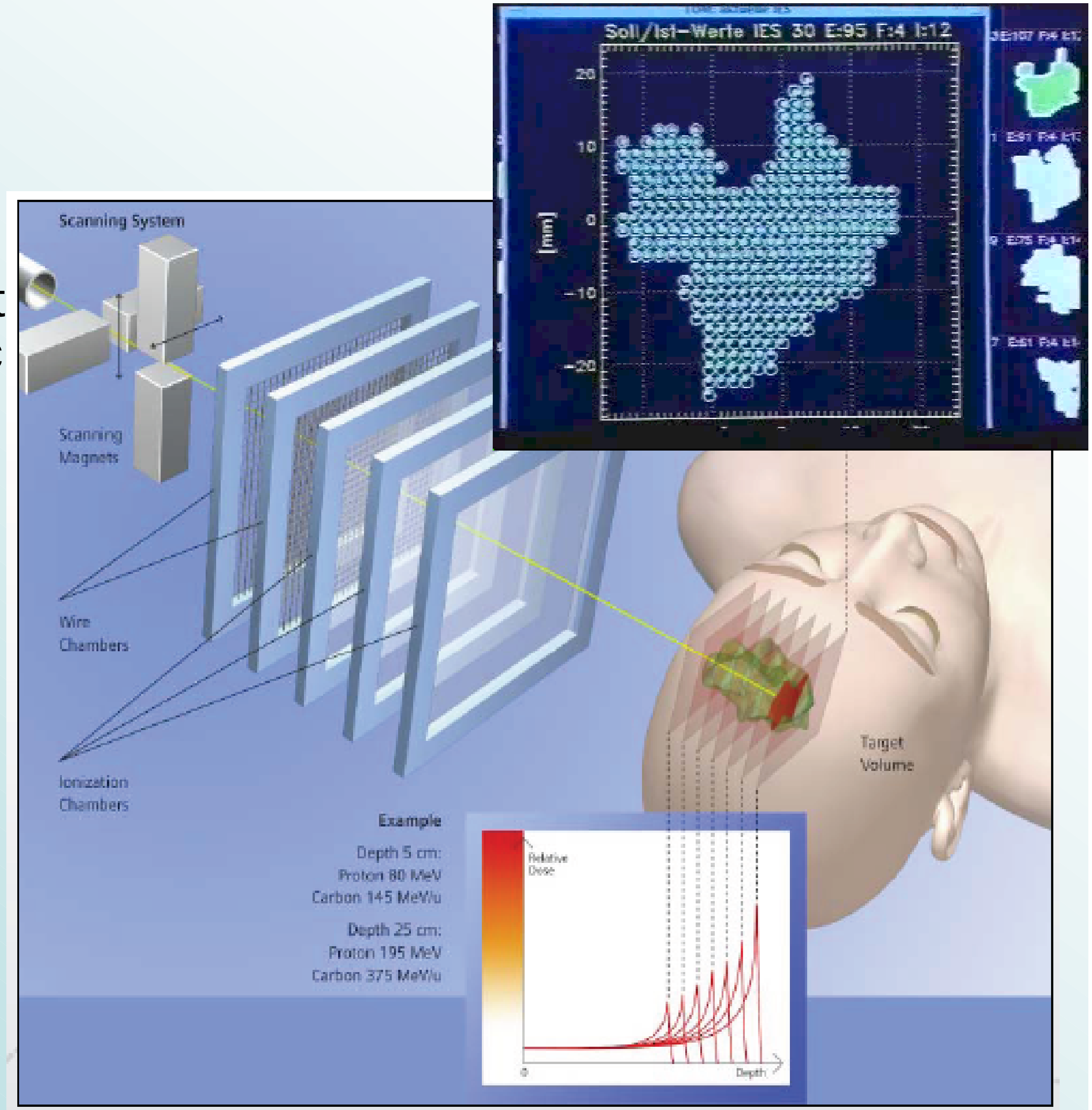
Optimized Treatment By Beam Scanning

Development in the 90ies:
Scanning techniques

a) Protons (Pedroni PSI): spot scanning gantry (1D magnetic pencil beam scanning) plus passive range stacking (digital range shifter)

b) Ions (Haberer et al.): raster scanning (2D magnetic pencil beam scanning) plus active range stacking (spot size, intensity) in the accelerator



Intensity-Controlled Rasterscan Technique, Haberer et al., GSI, NIM A,1993

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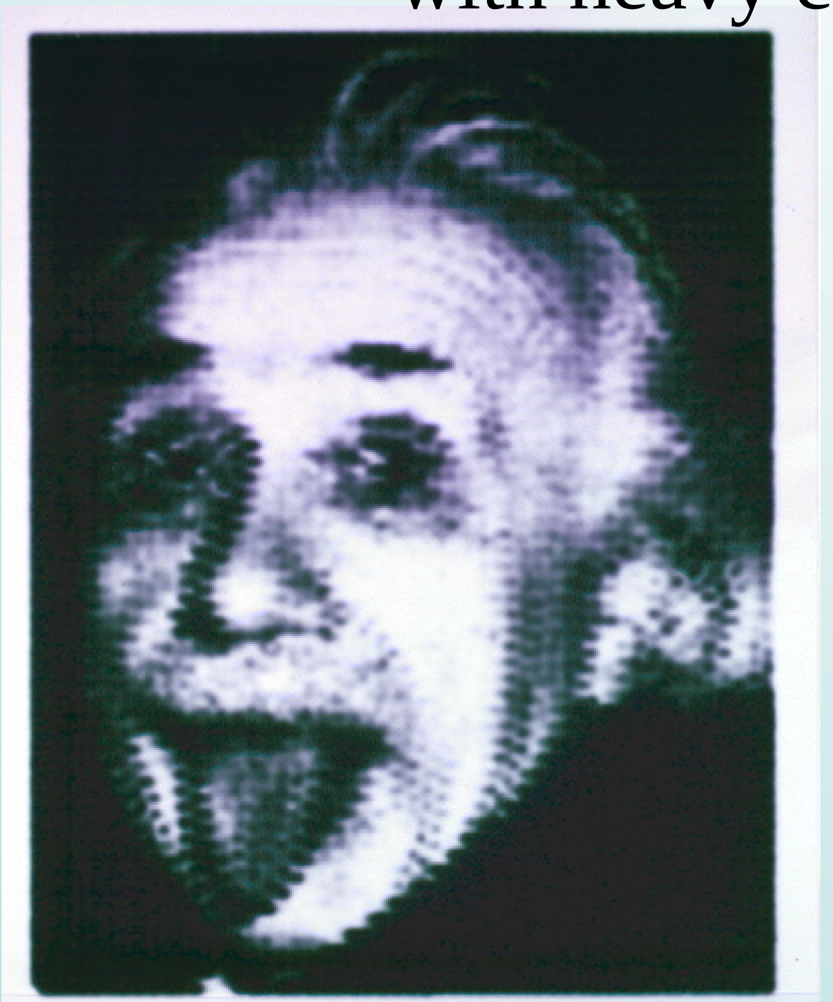
Intensity Controlled Raster Scanning with heavy charged particles:



Verification film irradiated with C-12 in 1996

<u>Clinical Experience:</u>

Protons:

PSI, CH: 450 patients

MDACC, MGH

Carbon-ions:

GSI, D: 440 patients

Clinical Feasibility

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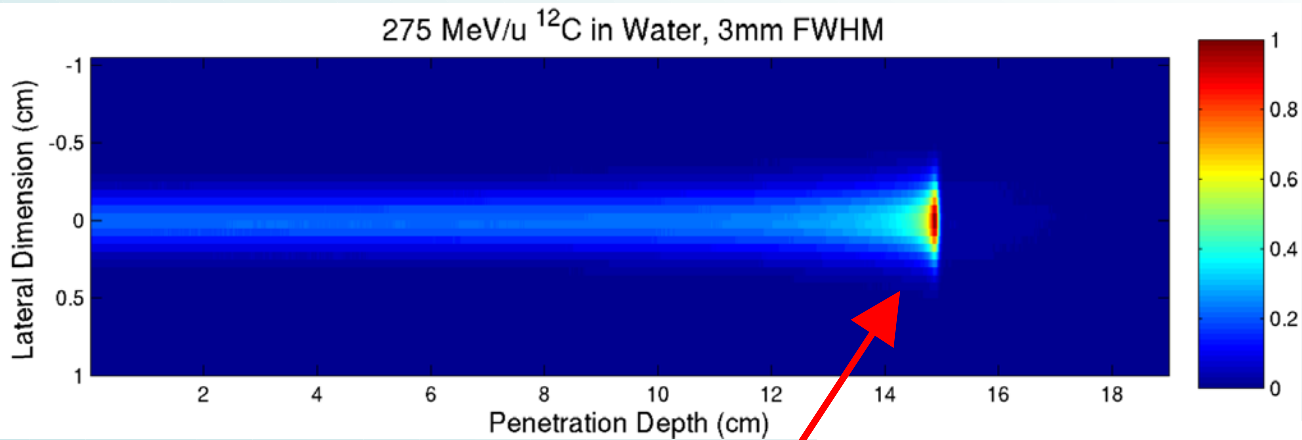
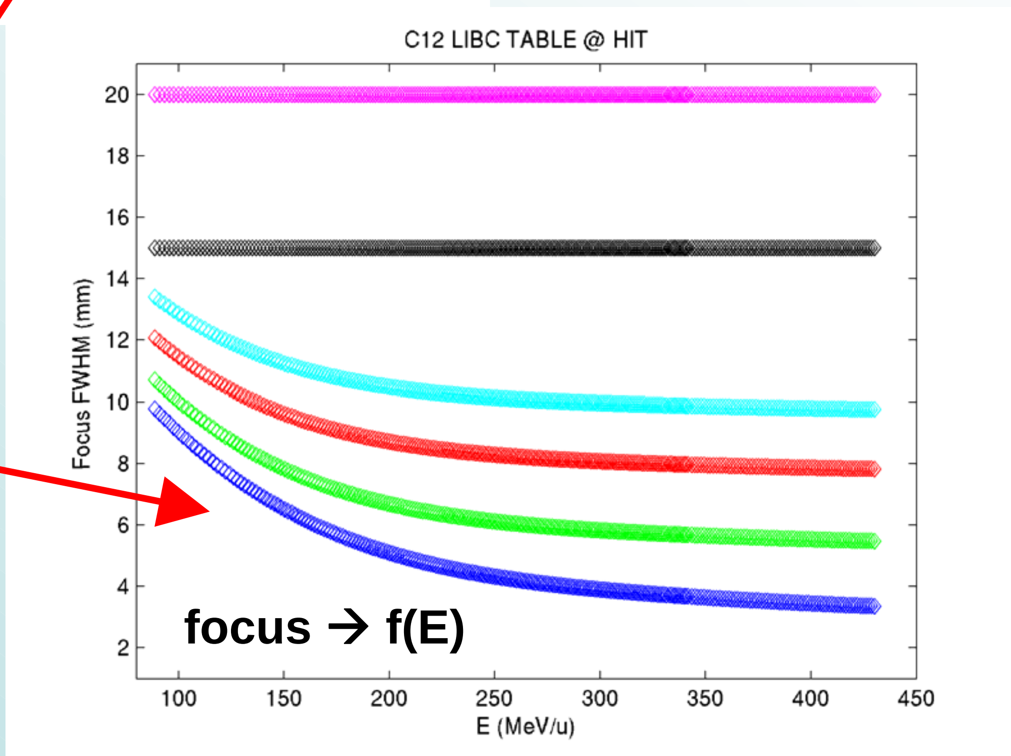
Challenge: Size Of The Beam, Precision, Time



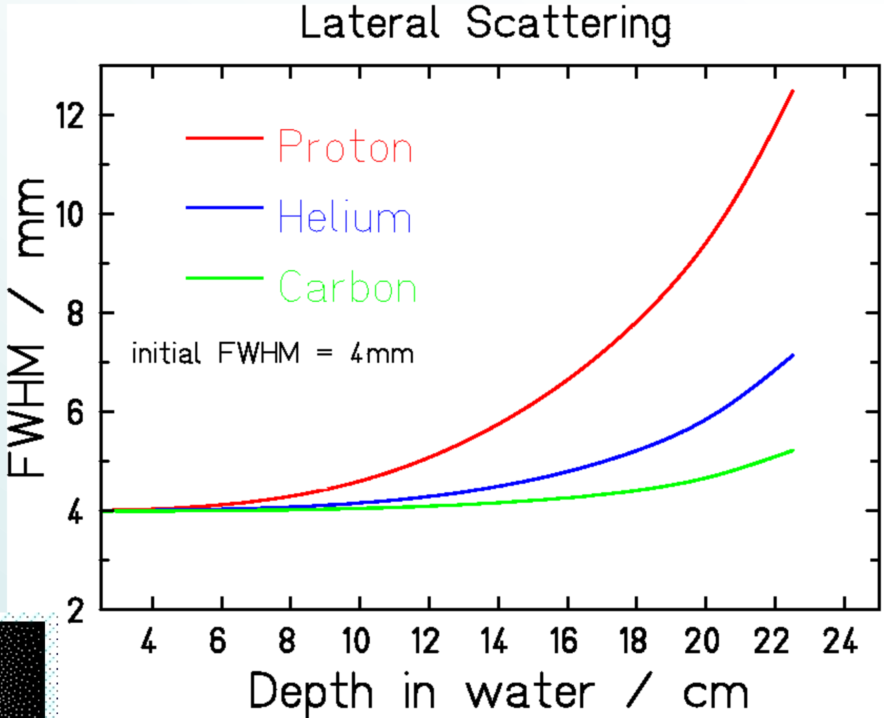
Straggling effects must be taken into account!

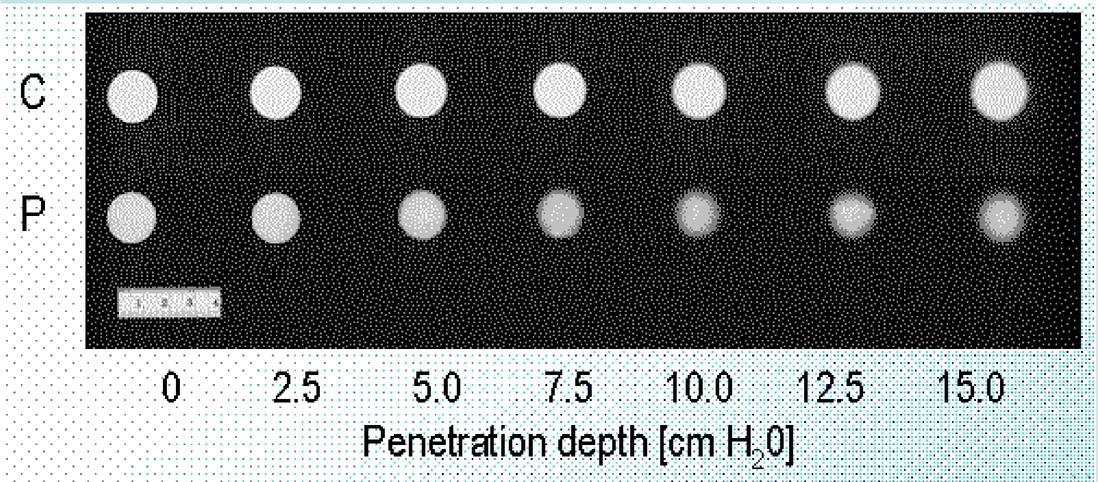
(vacuum window, dose monitoring system,…)



Beam Size

Higher local precision with carbon for deep-seated tumour treatment





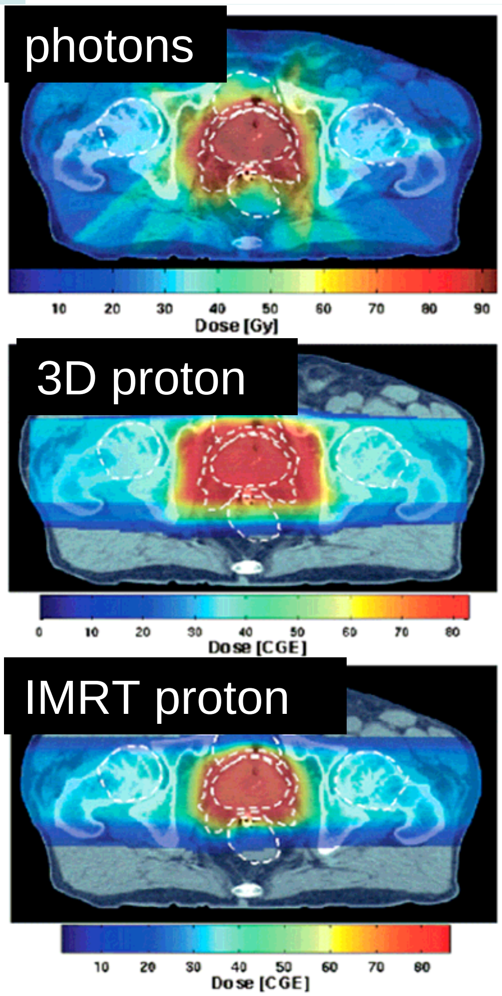
RADIOTHERAPY TREATMENT OF EARLY-STAGE PROSTATE CANCER WITH IMRT AND PROTONS: A TREATMENT PLANNING COMPARISON

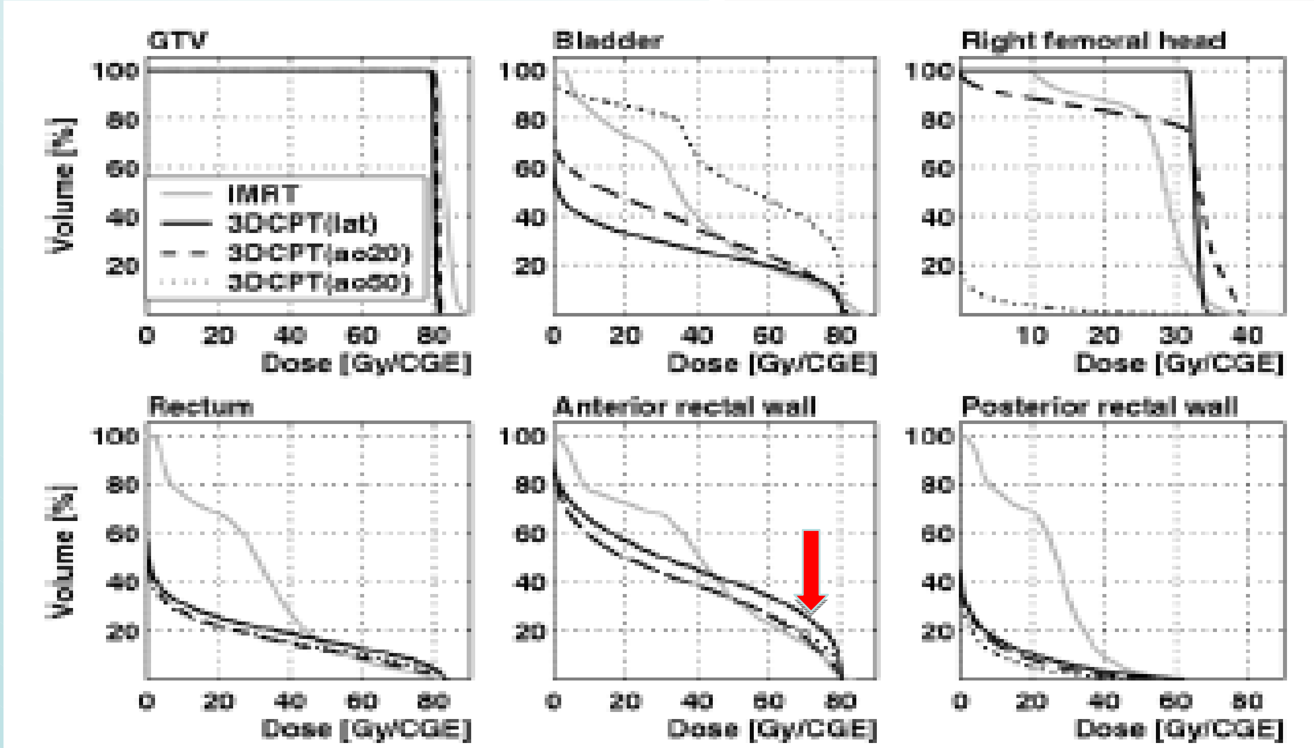
Alexei Trofimov, Ph.D., Paul L. Nguyen, M.D., John J. Coen, M.D., Karen P. Doppke, M.S., Robert J. Schneider, C.M.D., Judith A. Adams, C.M.D., Thomas R. Bortfeld, Ph.D., Anthony L. Zietman, M.D., Thomas F. DeLaney, M.D., and William U. Shipley, M.D.

Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA

Table 1. Treatment plan objectives

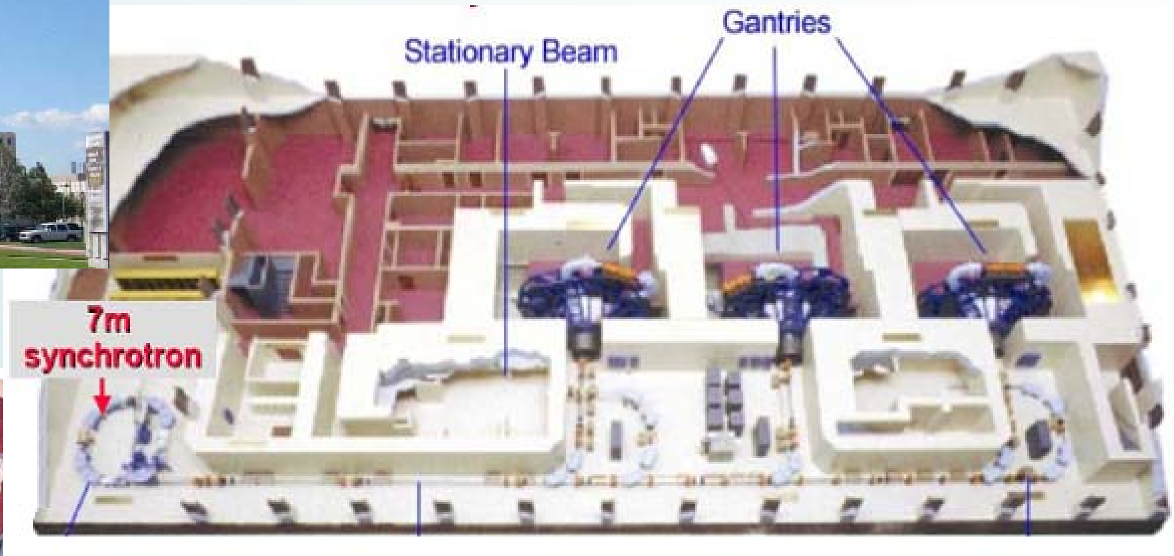
Target prescription doses	
GTV (prostate)	100% to 79.2 Gy/CGE
CTV (GTV and seminal vesicles)	100% to 50.4 Gy/CGE
PTV2 (GTV + 5-mm margin)	98% to 79.2 Gy/CGE
PTV1 (CTV + 5-mm margin)	98% to 50.4 Gy/CGE
Tolerance doses for healthy organs	
Rectum	<50% to 60 Gy/CGE
	<35% to 65 Gy/CGE
	<25% to 70 Gy/CGE
	<15% to 75 Gy/CGE
	Maximum 84.7 Gy/CGE
Bladder	<50% to 65 Gy/CGE
	<35% to 70 Gy/CGE
	<25% to 75 Gy/CGE
	<15% to 80 Gy/CGE
	Maximum 84.7 Gy/CGE
Femoral head	Maximum 50 Gy/CGE
Penile bulb	Mean dose < 52.5 Gy/CGE

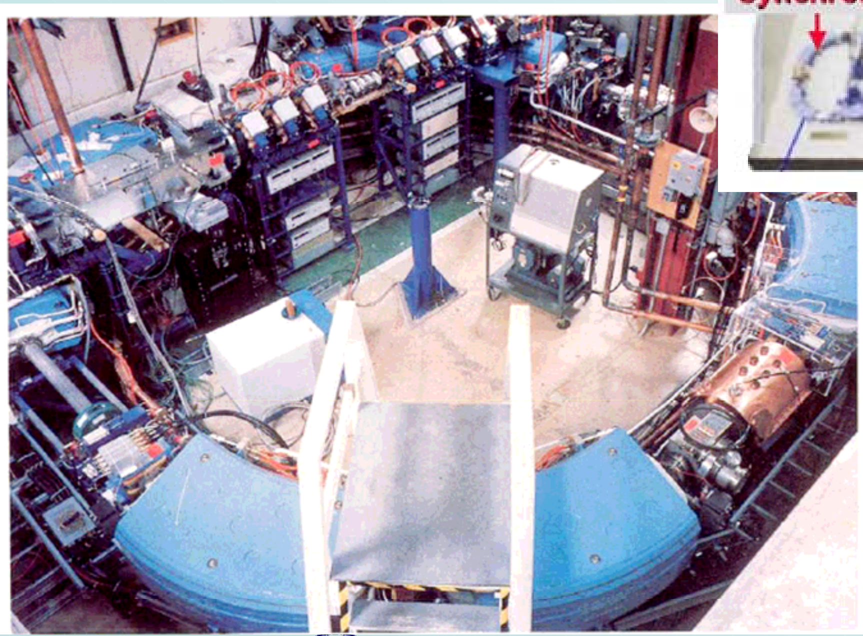




First Hospital Based Particle Therapy Facility – Loma Linda/USA

13,500 patients treated





1st hospital based proton therapy centre (since 1990) using a synchrotron – designed and commissioned by Fermilab
2005: 160 sessions/day

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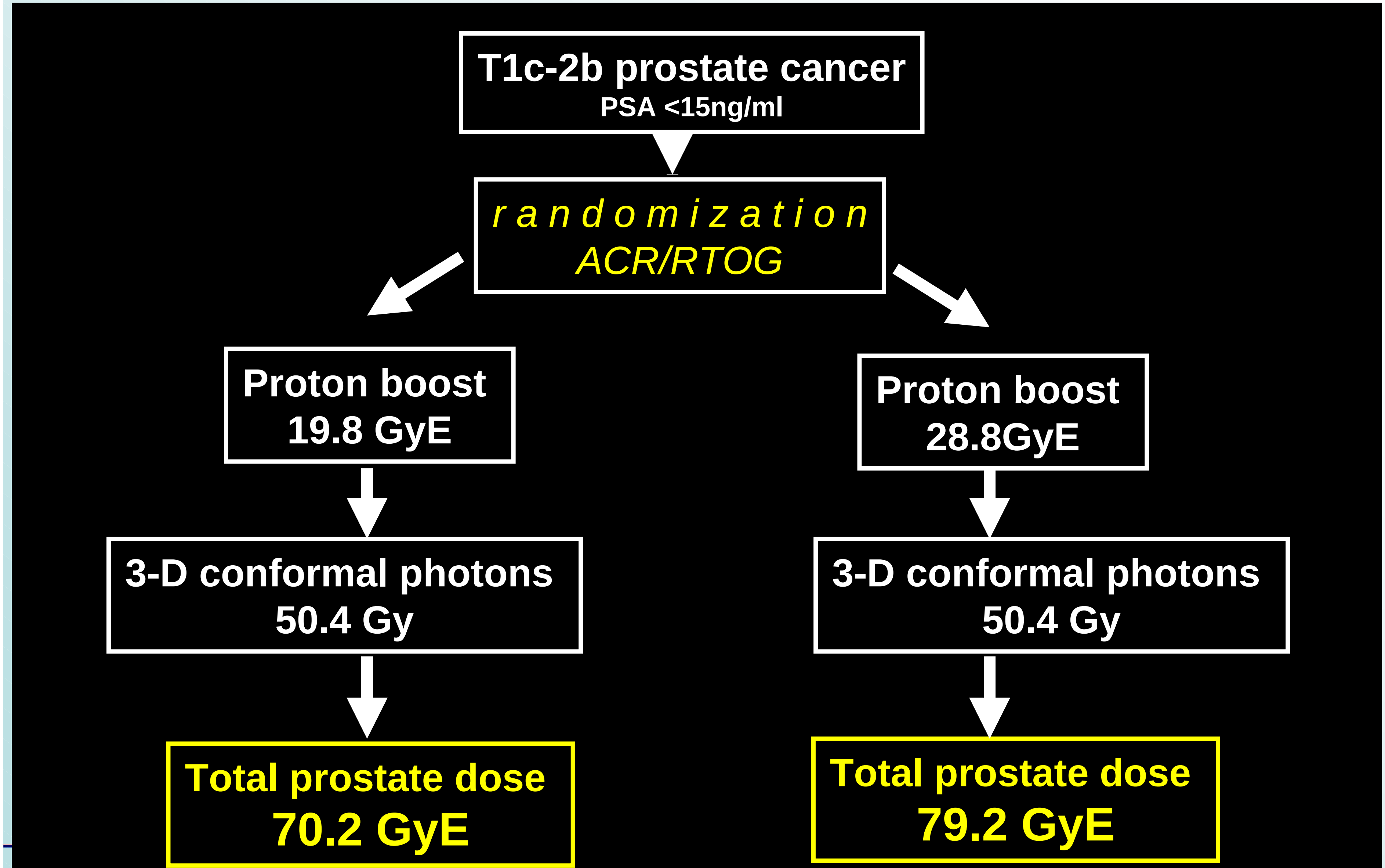
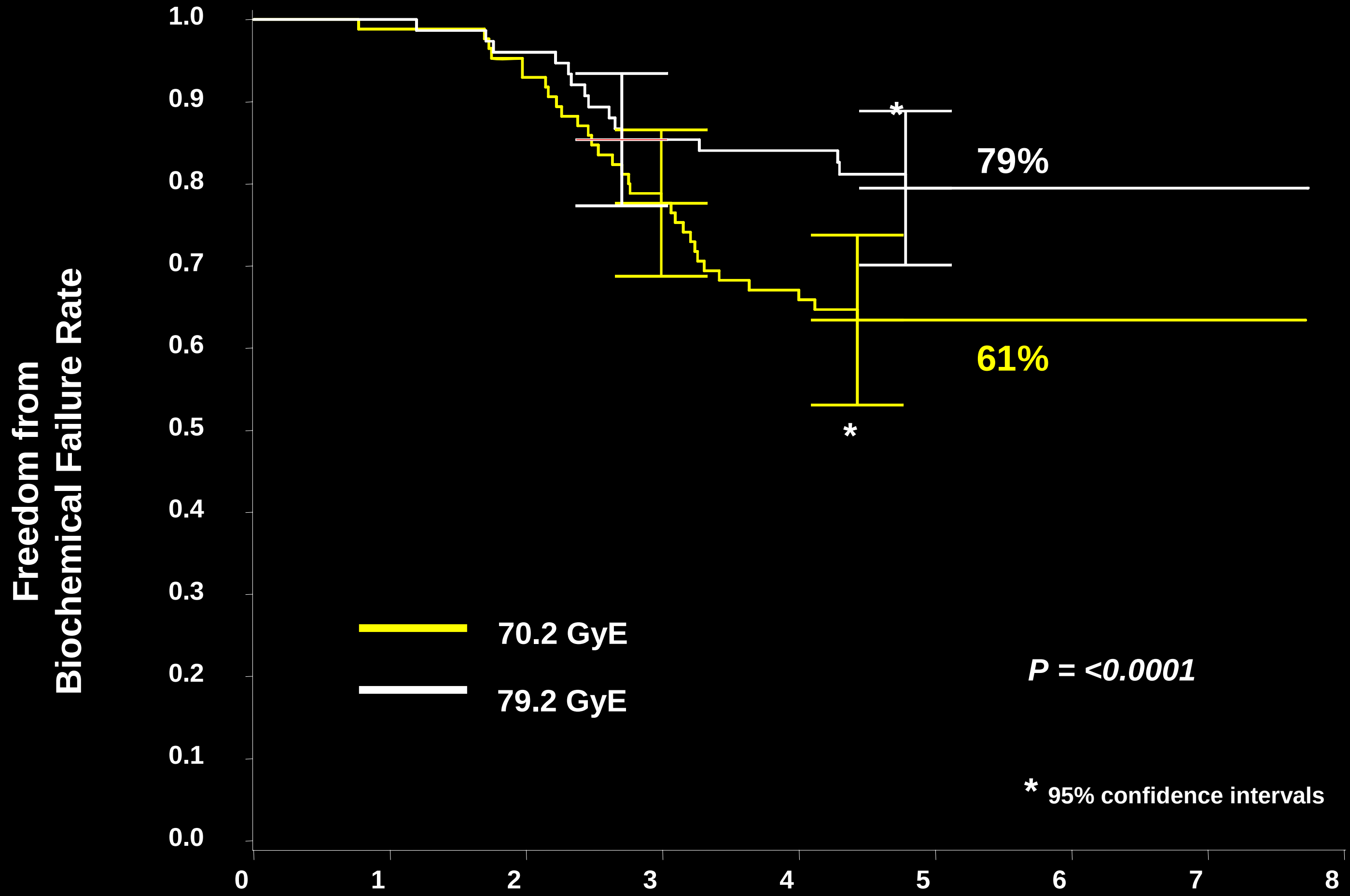
Study Of Protontherapy In Patients With Prostate Cancer (PROG 9509)



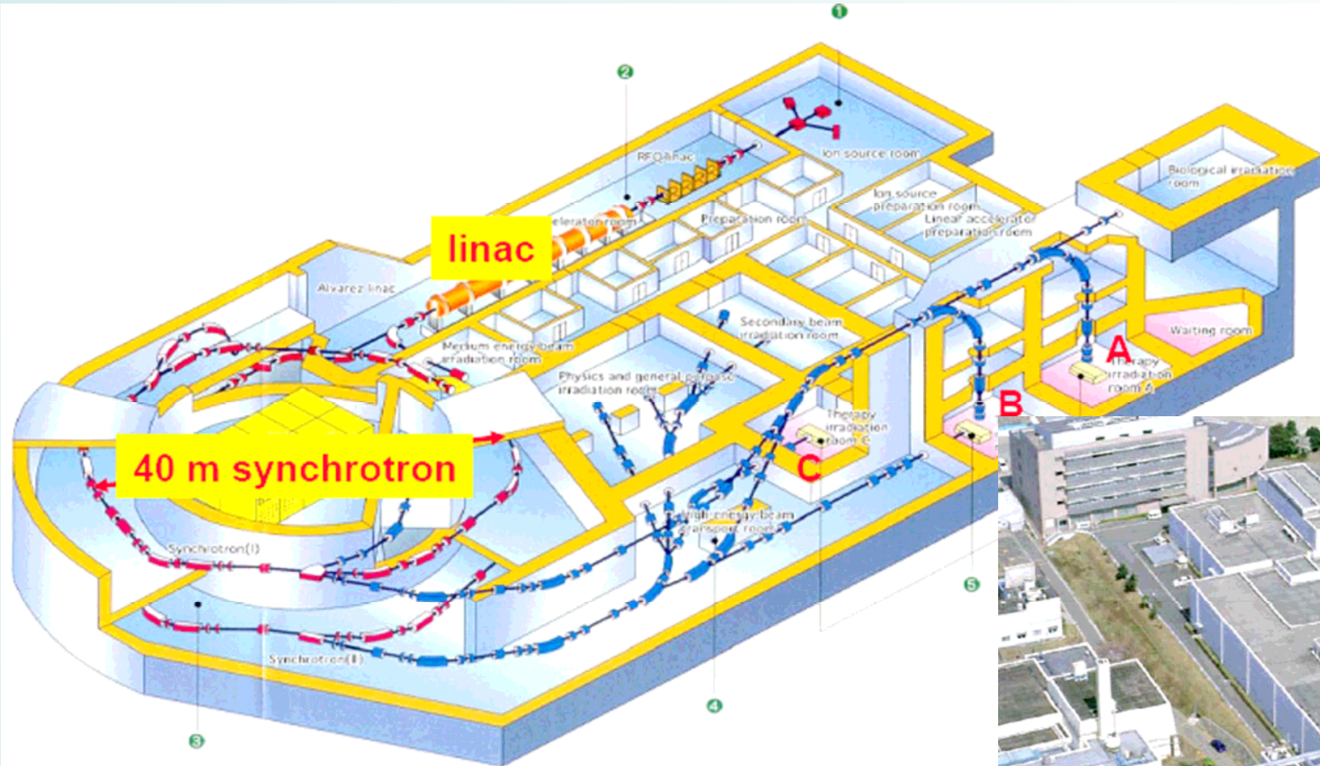
Improved Freedom from Biochemical Failure (PSA)



# at risk									
70.2 GyE (yellow)	197	196	171	139	118	76	31	10	10
79.2 GyE (white)	195	194	184	163	148	99	46	20	2

Zietman et al 2005

Particle Therapy Facilities – HIMAC/Japan



The Heavy Ion Medical Accelerator of NIRS (since 1994)

Two identical 800 MeV/u synchrotrons for ions up to Argon; mainly Carbon is used

4,500 patients treated

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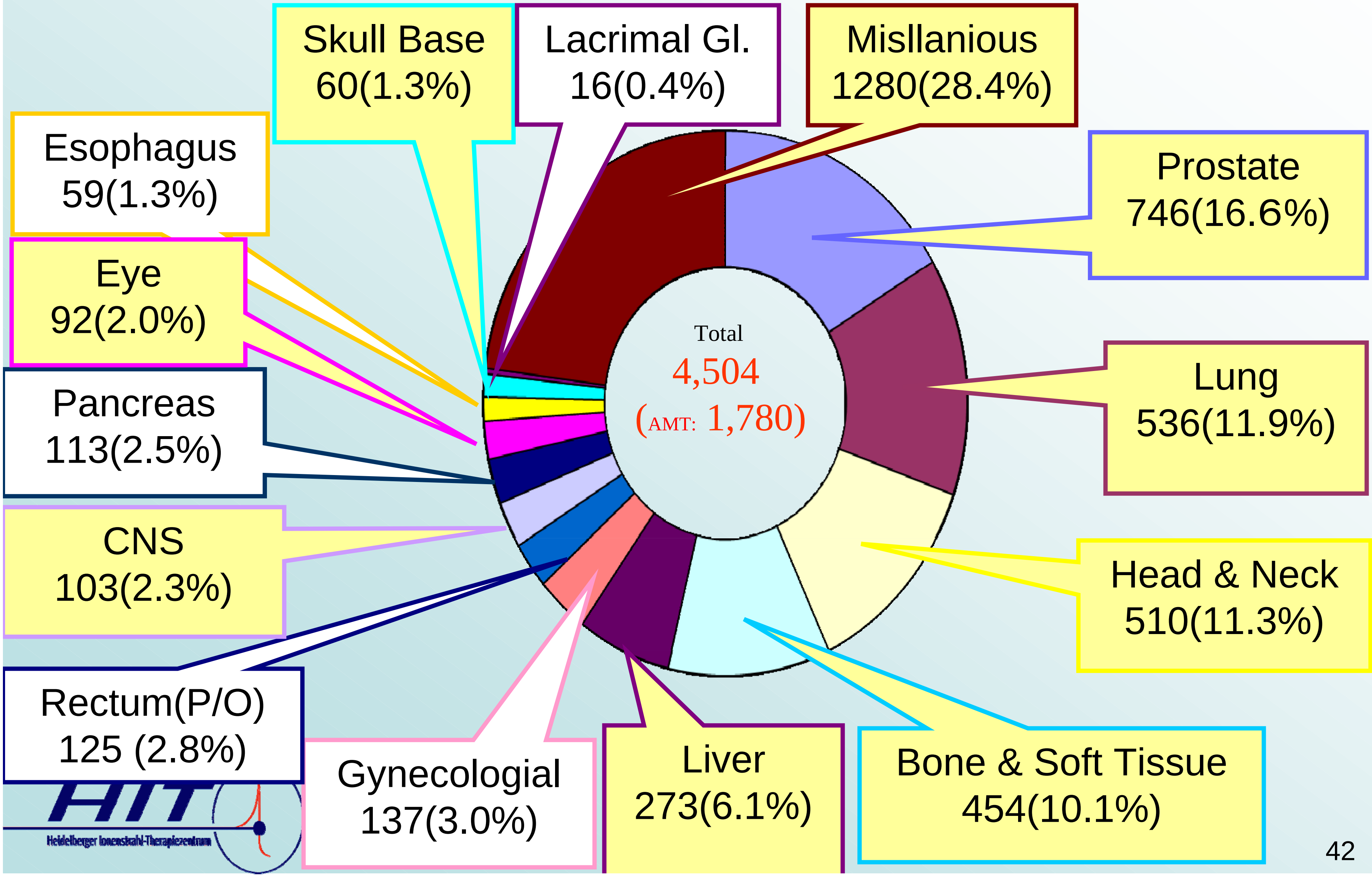
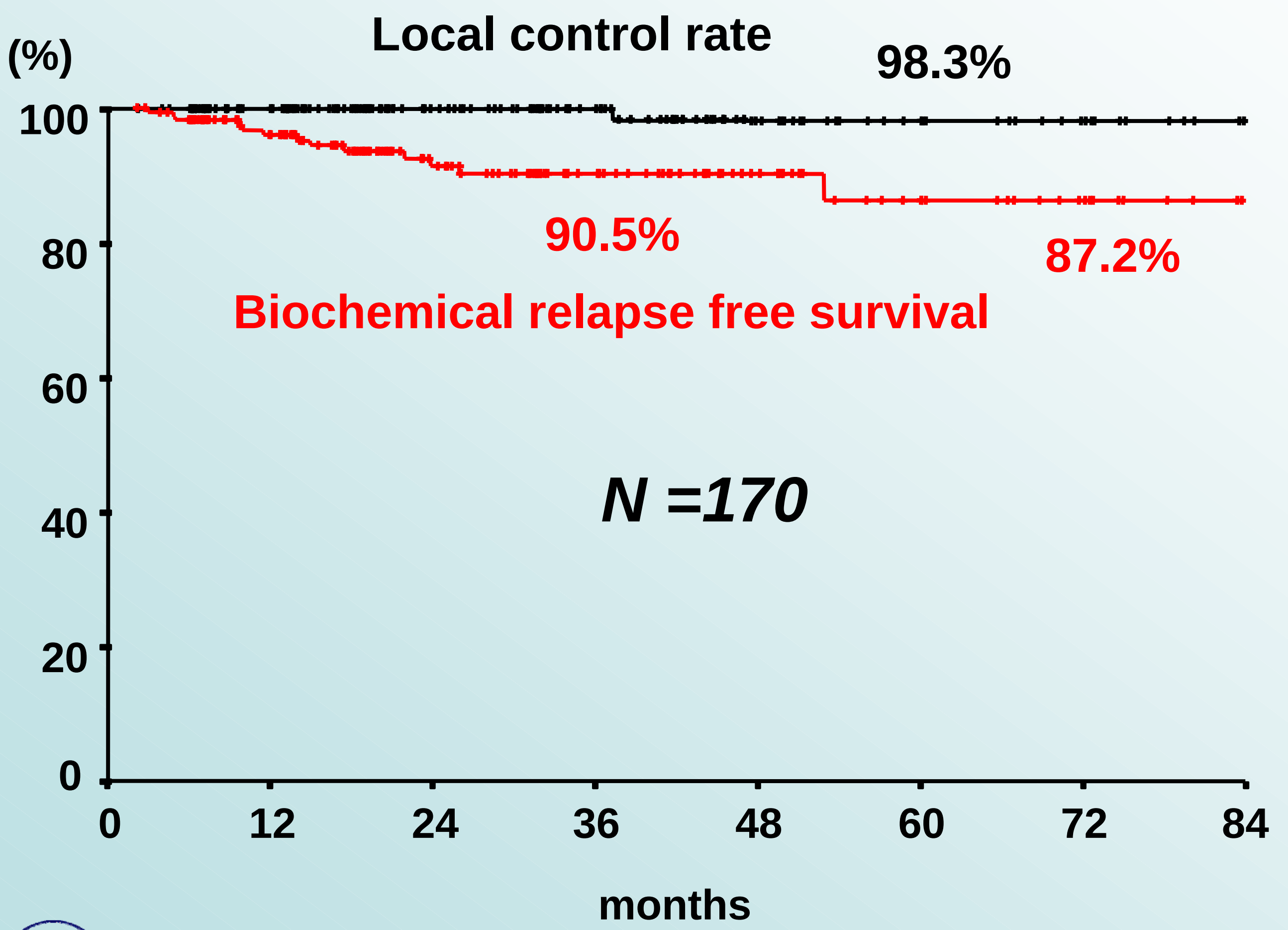
Patients enrolled into Carbon Ion Radiotherapy CHIBA
(June 1994 ~ February 2009)



Local Control & Biochemical Relapse Free Rates
Prostate Cancer (Japan)



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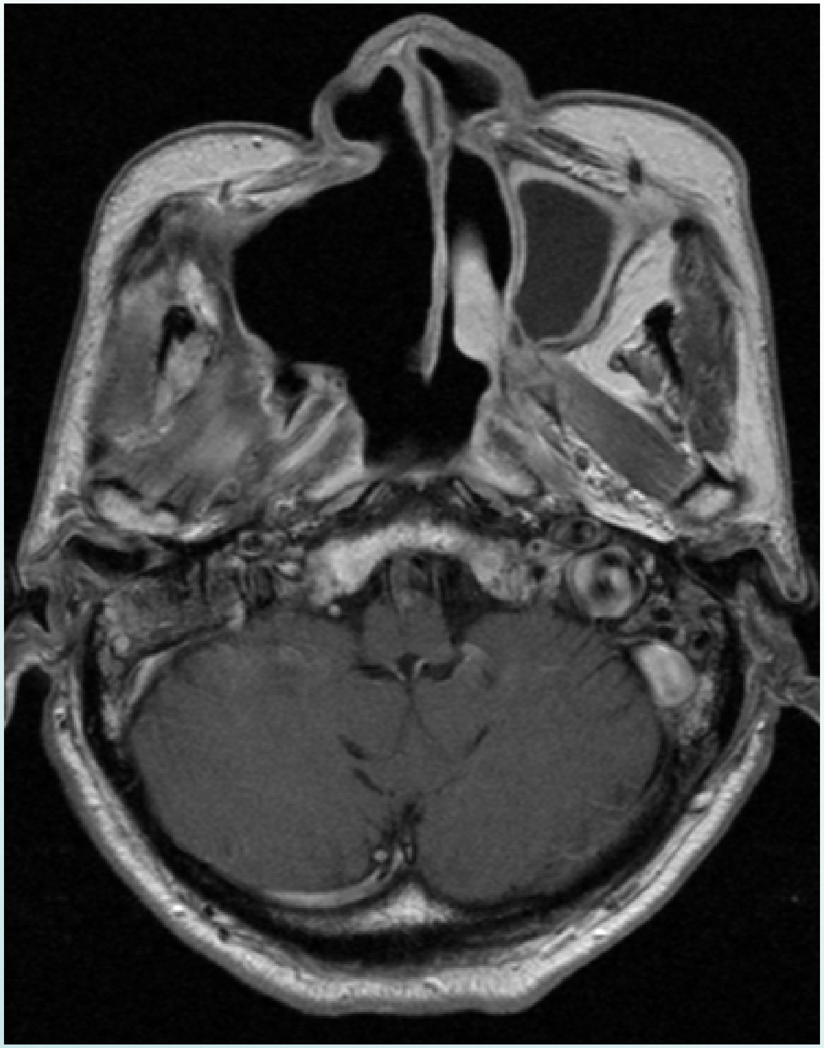
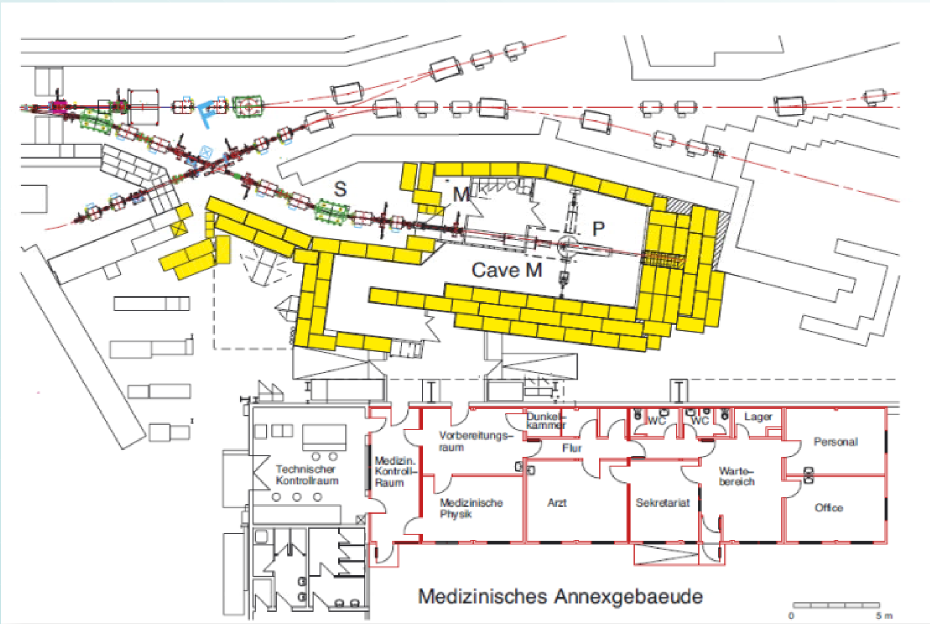
Patient mit inoperablem malignen Melanom 57.6GyE/16fx

vor RT



48 Monate nach RT

Particle Therapy Facilities – HIT/Heidelberg



HIT concept and layout is based on experience from GSI; 448 patients were treated with carbon beams from 1997 – 2008 using raster scanning technique

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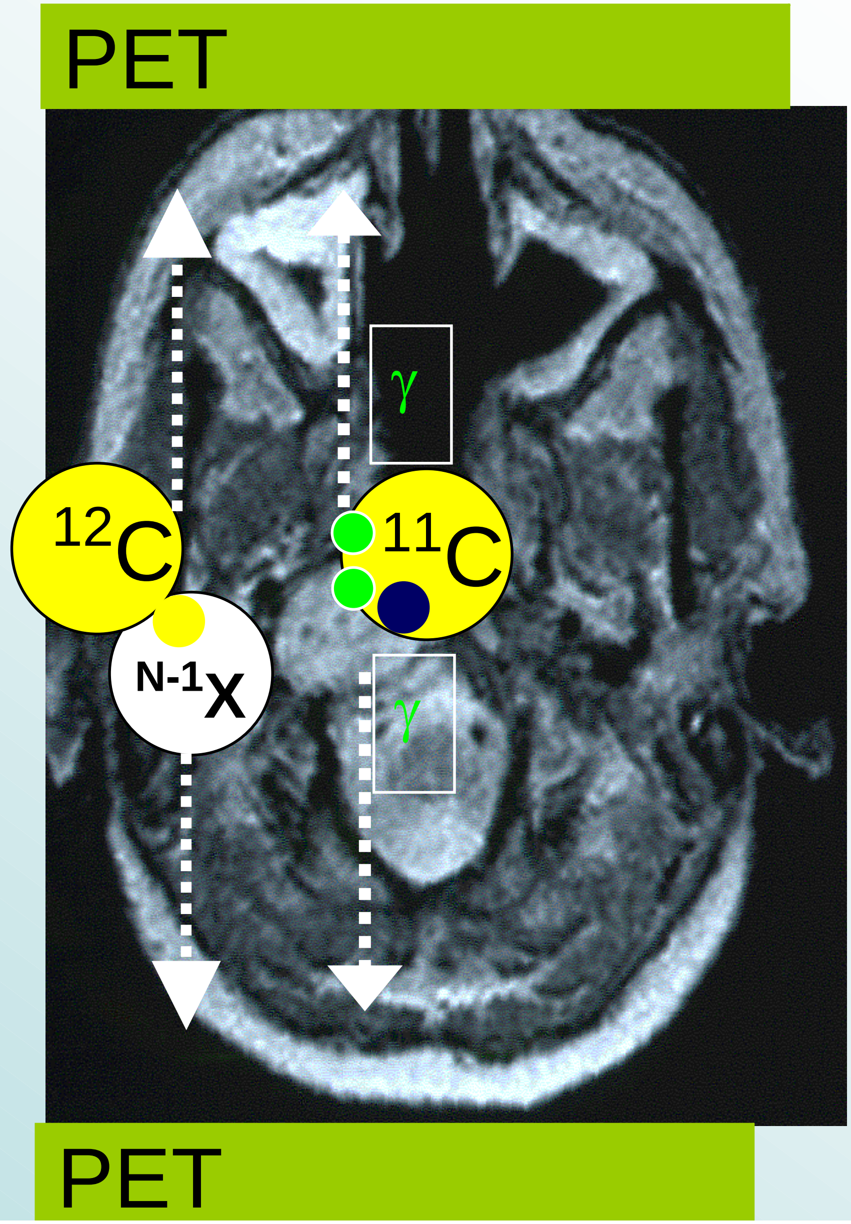
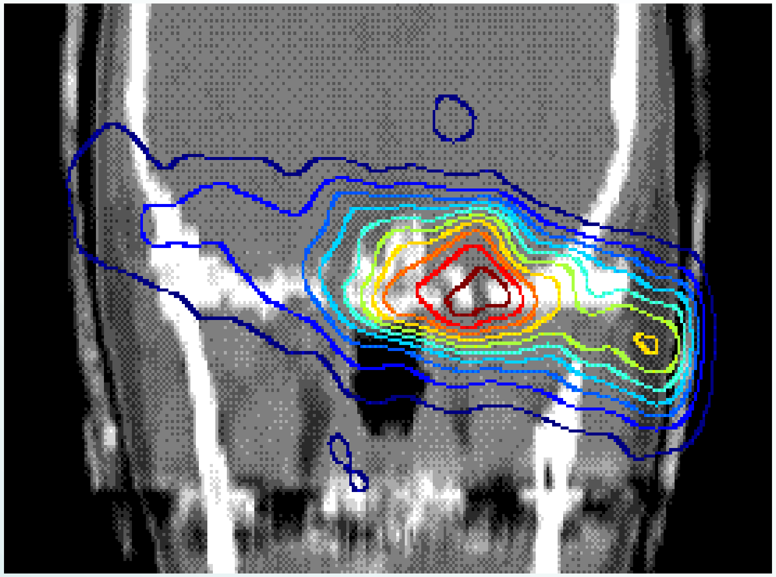
Principle of in-situ PET



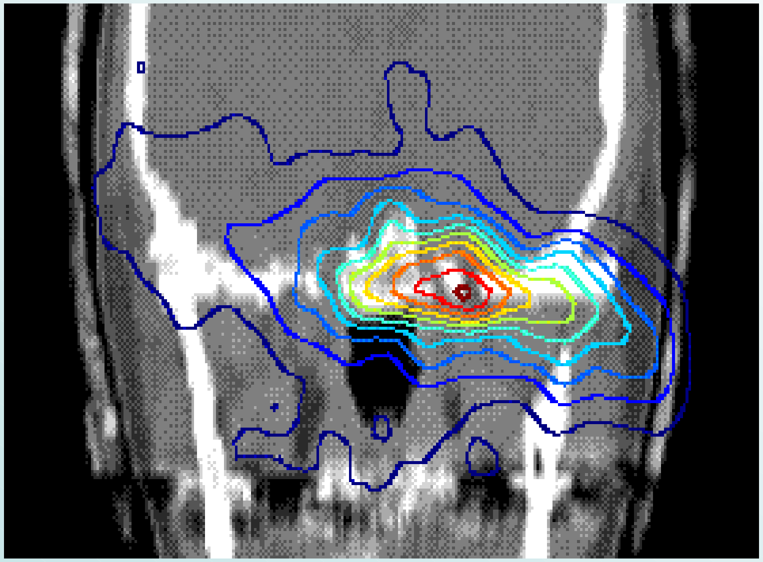
Verification with PET

Patient during treatment

Expected PET

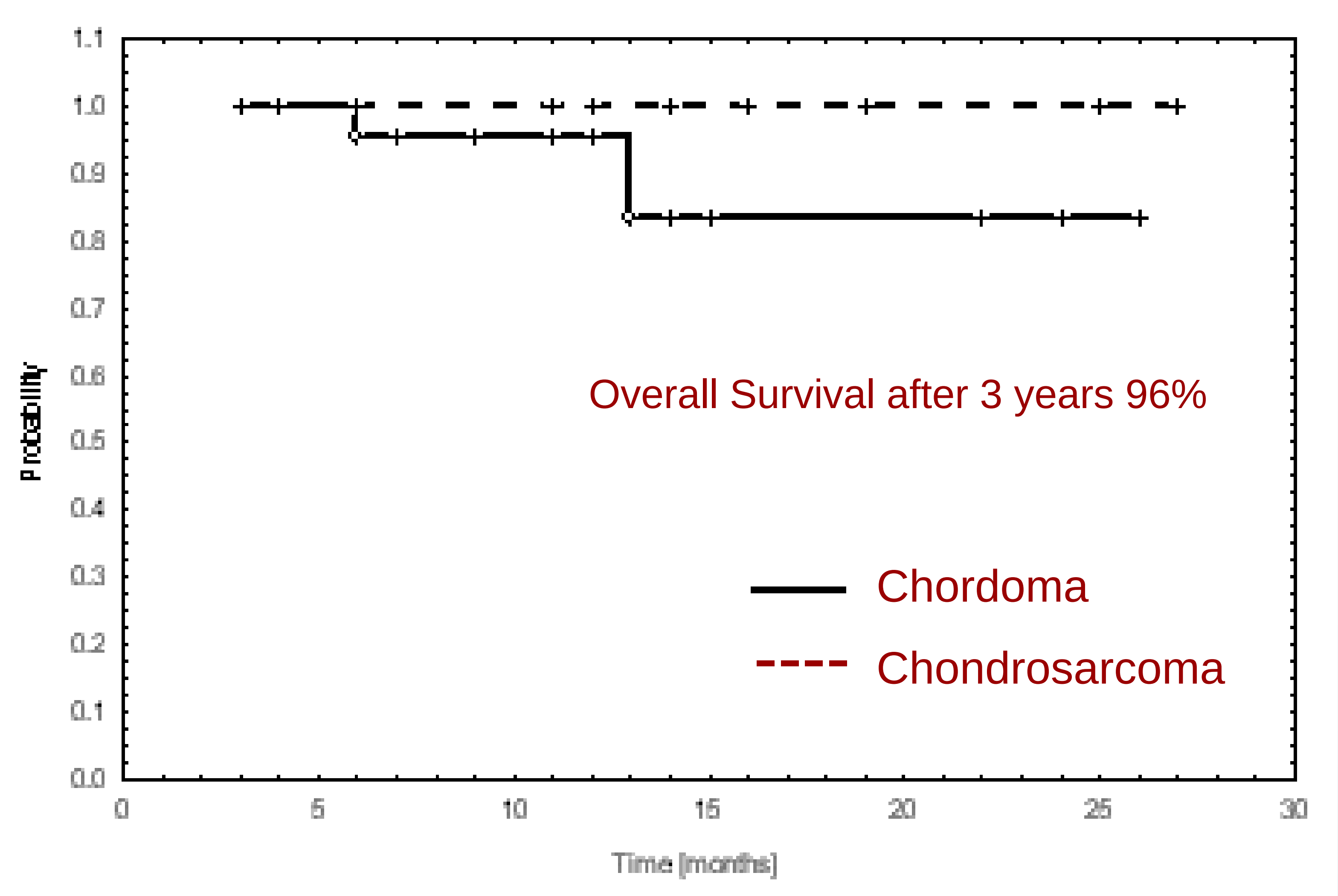


PET-Measurement



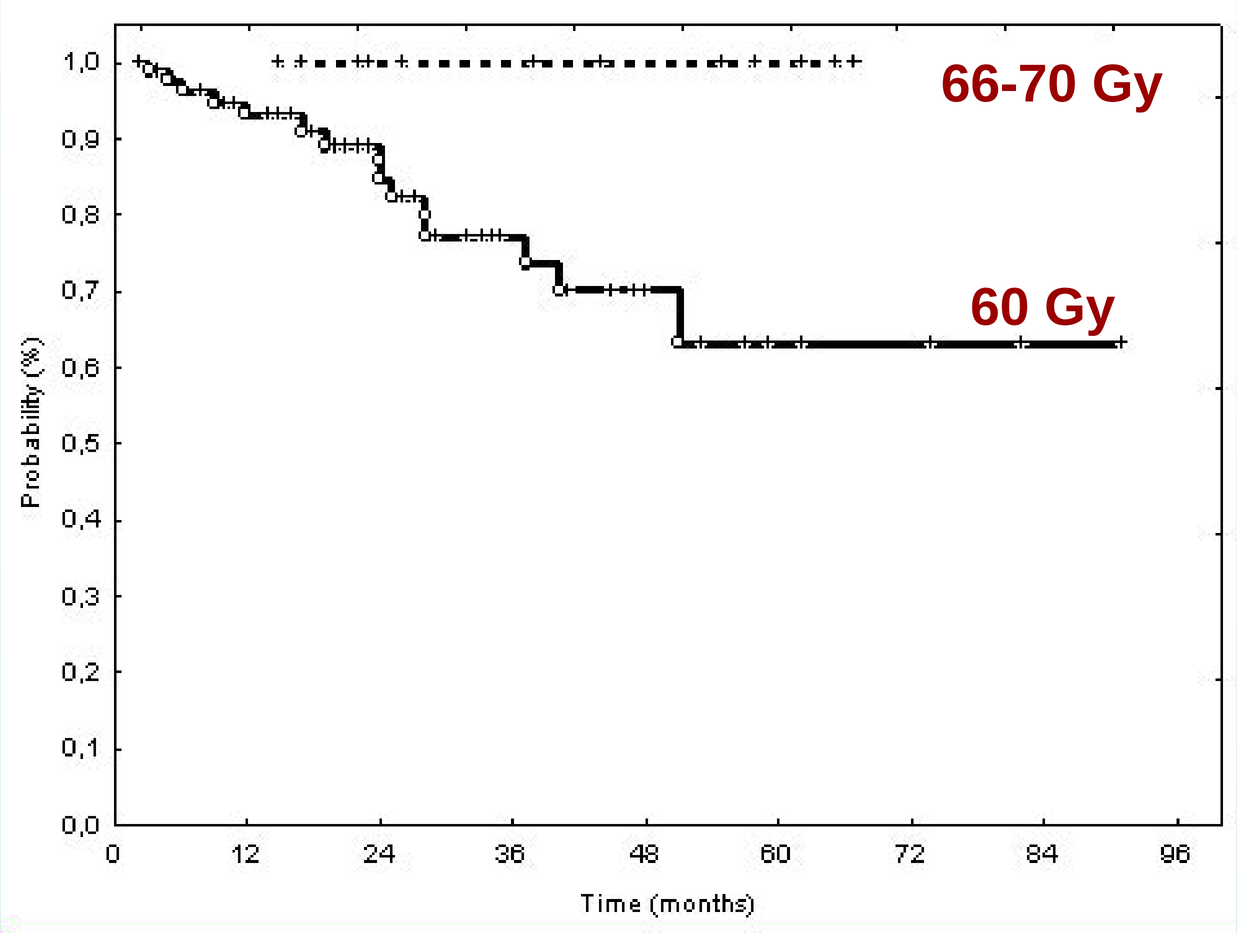
Progressionfree Survival

Chordoma / Chondrosarcoma G1/2 n=67 (Phase II Study)

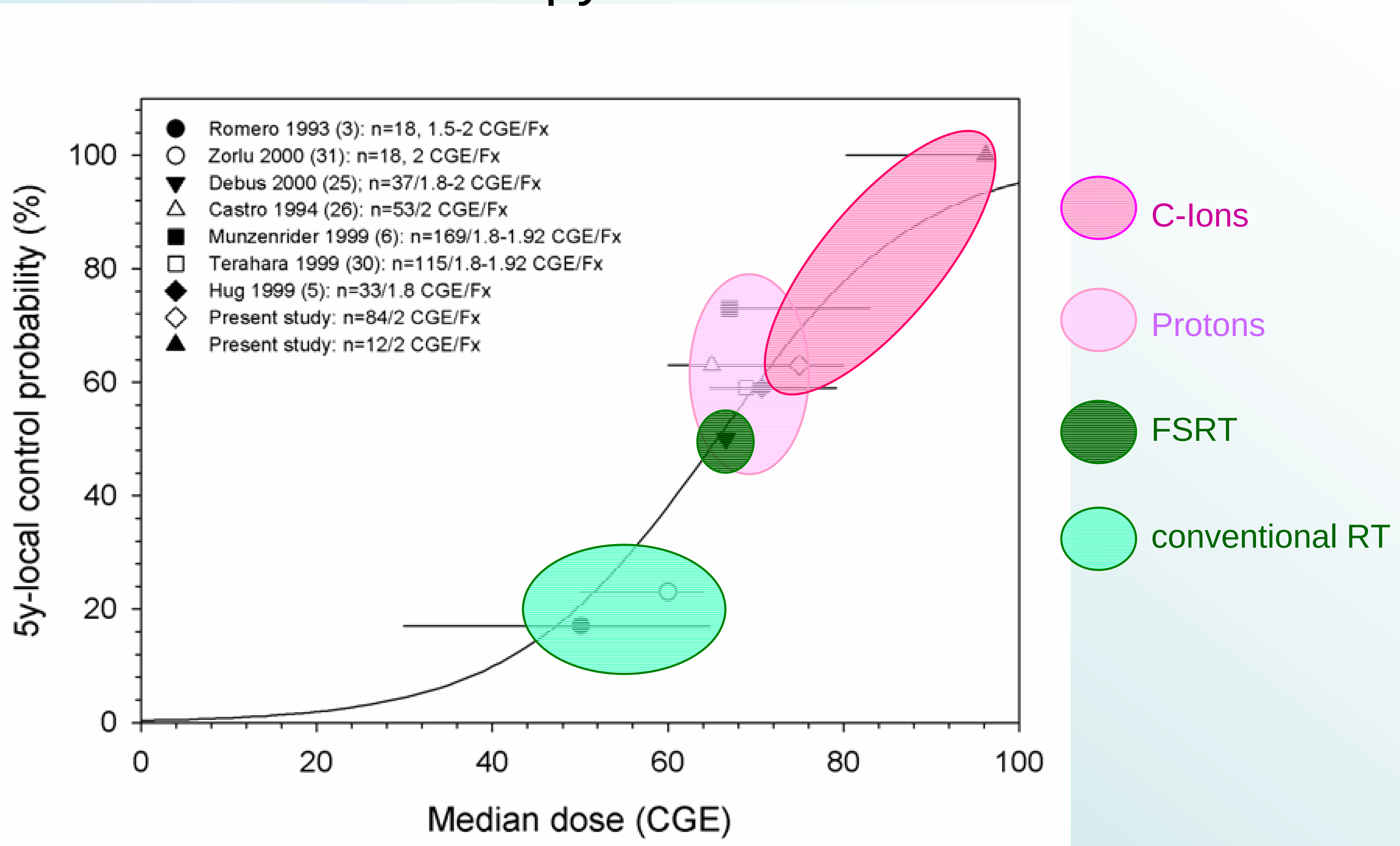


Local Tumor Control

Chordome n=91 (Dose =60 Gy vs > 60 Gy)

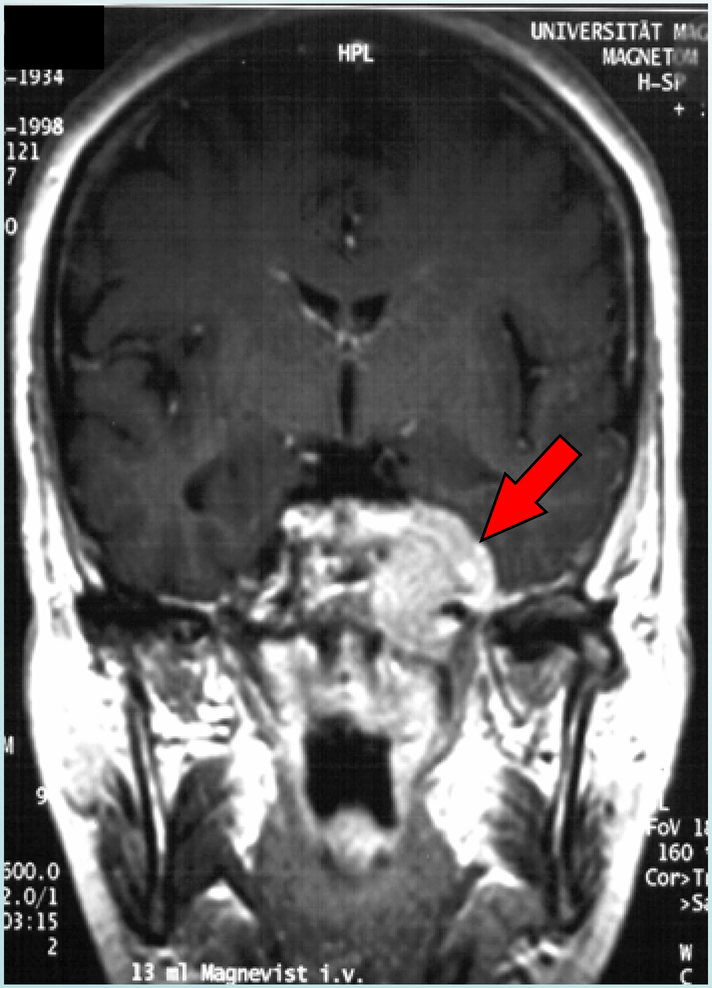


Motivation: Dose Response Relationship Radiotherapy of Skull Base Chordomas

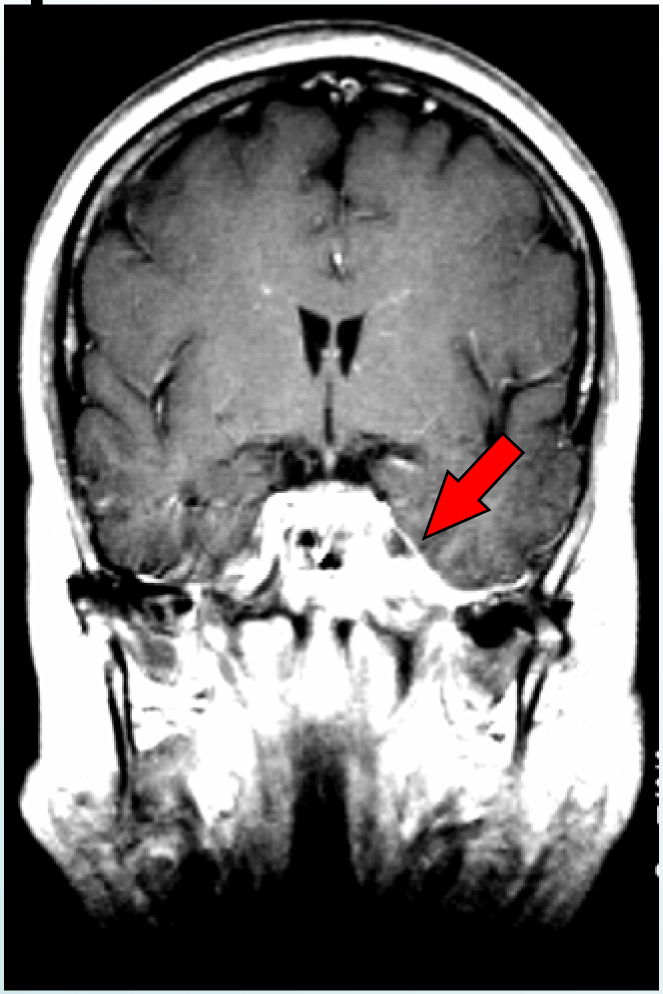


[Schulz-Ertner, IJROBP 2007]

Adenoidzystic Carcinoma: Follow-up



Before C12-RT



6 Weeks after RT

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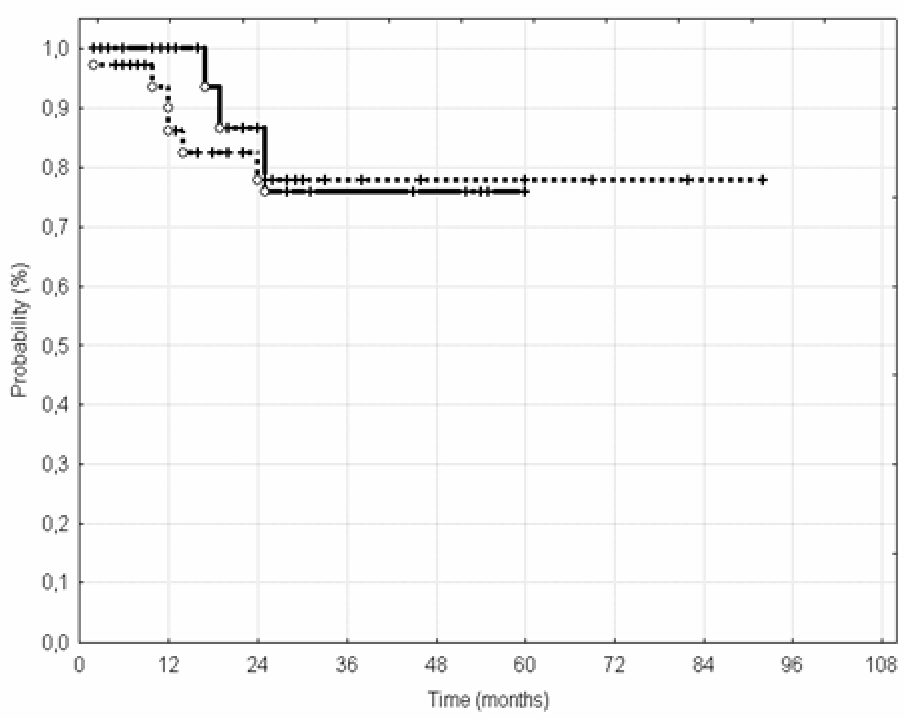
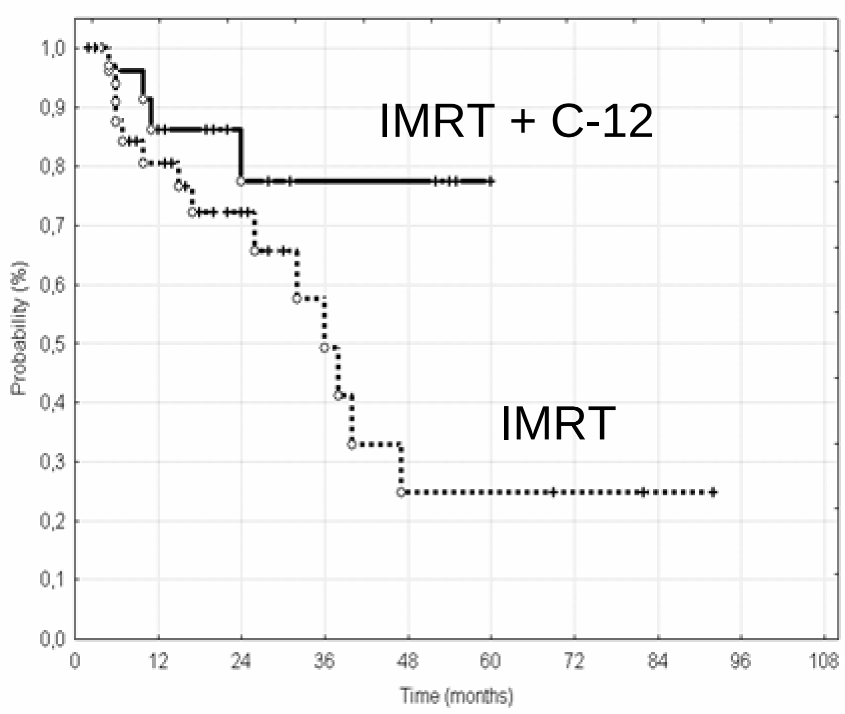
FSRT / IMRT vs. FSRT / IMRT + C12
locally advanced adenoidcystic carcinoma



Overall Survival



Local Control

- **no dose limiting acute toxicity**
- **late toxicity > CTC grade 2 < 5%**

Schulz-Ertner, Cancer. 2005 Jul 15;104(2):338-44

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First Stone Ceremony Of HIT:

May, 2004

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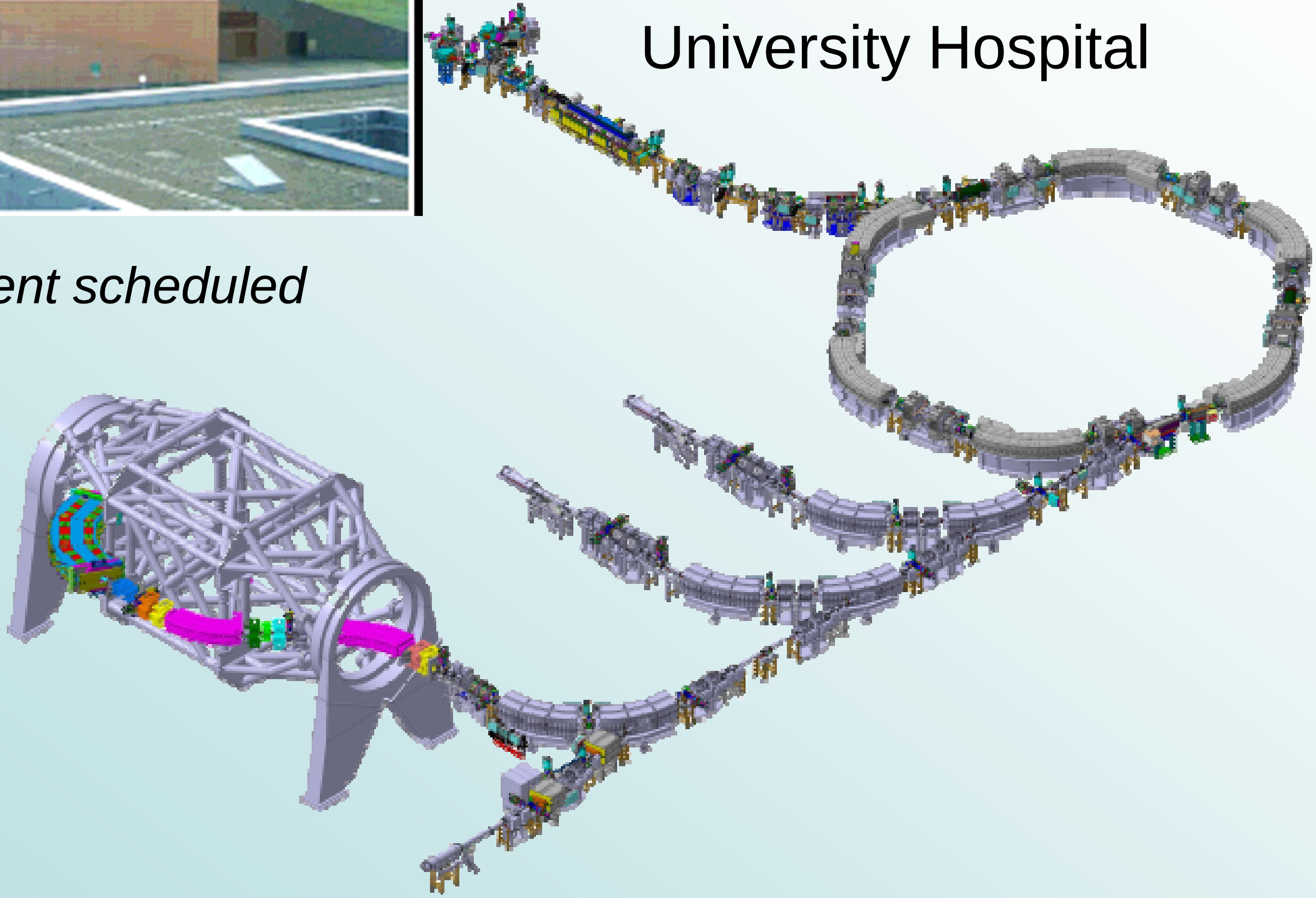
Accelerator On Campus
facilitating clinical and translational research

Strong partners joint forces @HIT: university HD, NCT, dkfz, GSI

Particle Therapy Facilities – HIT/Heidelberg

Compact building (60 x 70 m², 3 levels), directly linked to the "Head Clinics" of the University Hospital

Start of patient treatment scheduled in 2 weeks



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Particle Therapy Facilities – HIT/Heidelberg

Worldwide first isocentric ion gantry – including a scanning system:

Ø = 13m
25m long

600 tons overall weight

0.5 mm max. deformation

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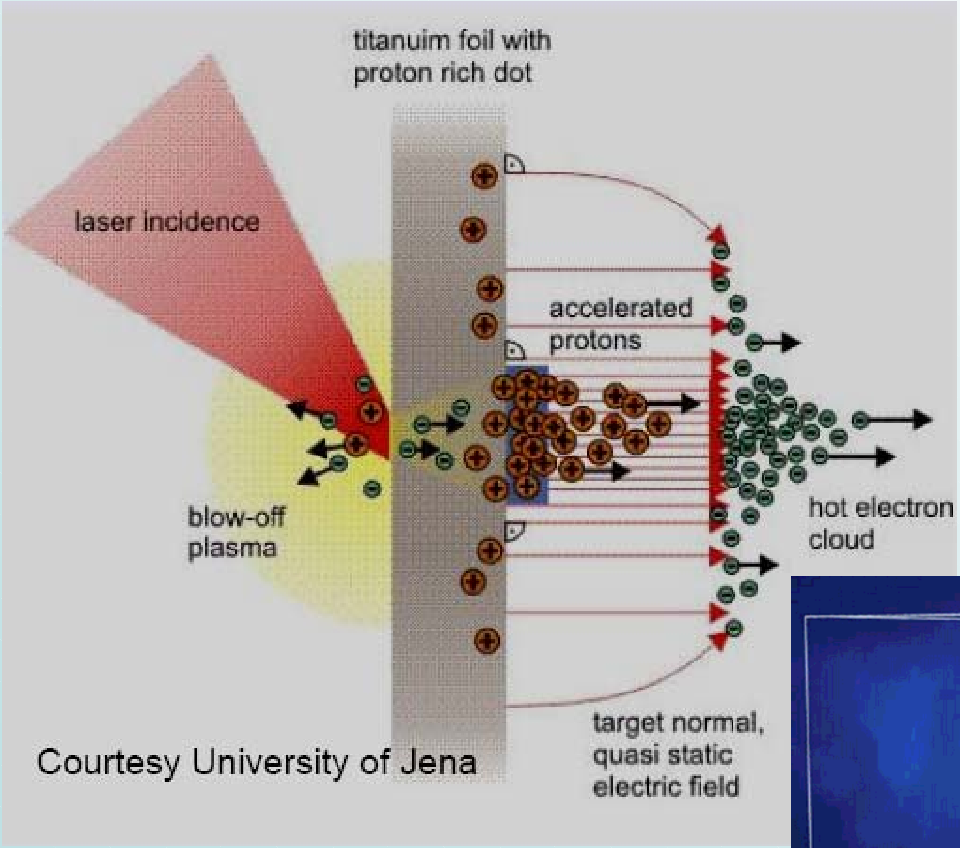
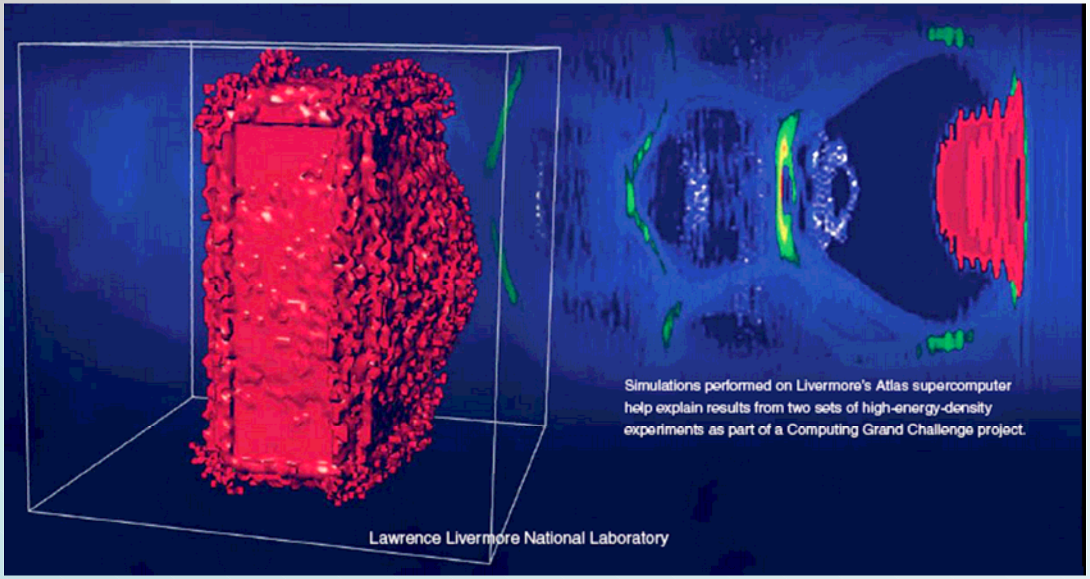
New concepts – laser plasma accelerators



- **Laser: 50 fs, 50 J (Petawatt!)**
- **$I = 10^{21}$ W/cm^2**
- **10^{11} protons up to 300 MeV should be possible**

- **Repetition rate?**
- **Intensity control?**



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New concepts – Dielectric wall accelerators

G. Caporaso et al, LLNL

250 MeV protons in 2.5 m?

Pulse-to-pulse energy & intensity variation

"Hoping to build a full-scale prototype soon"

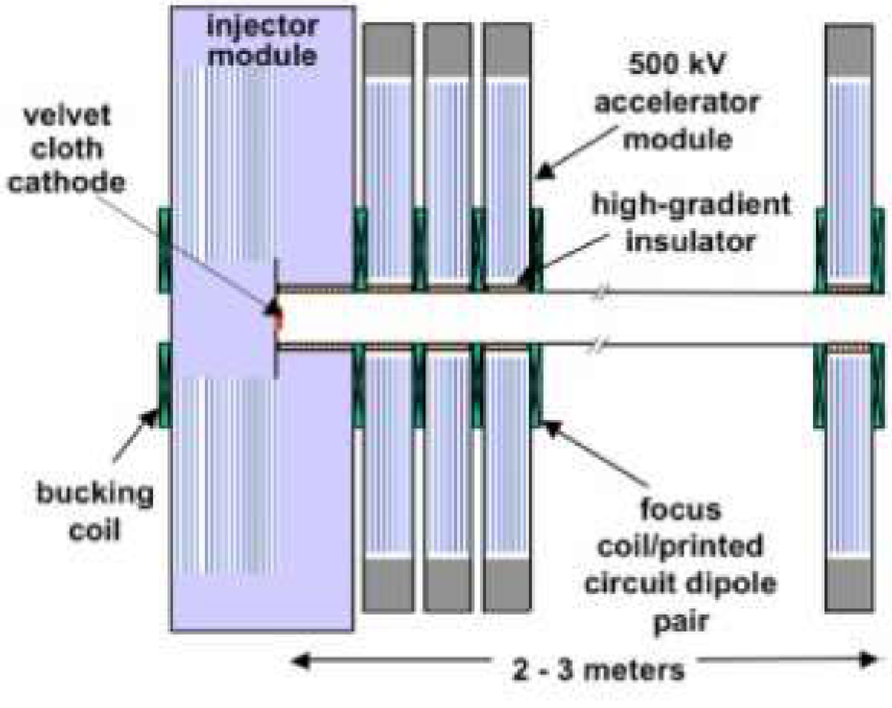
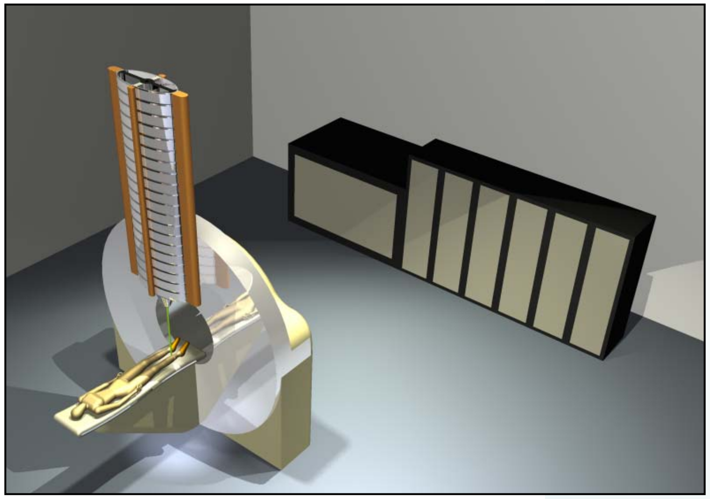
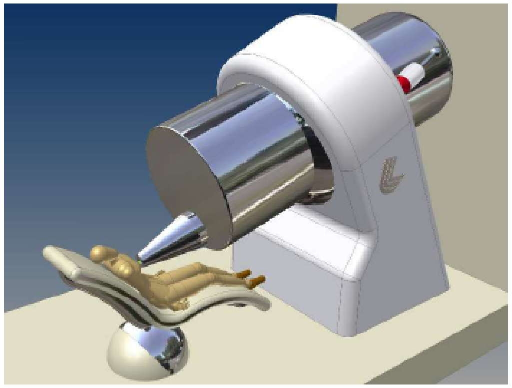


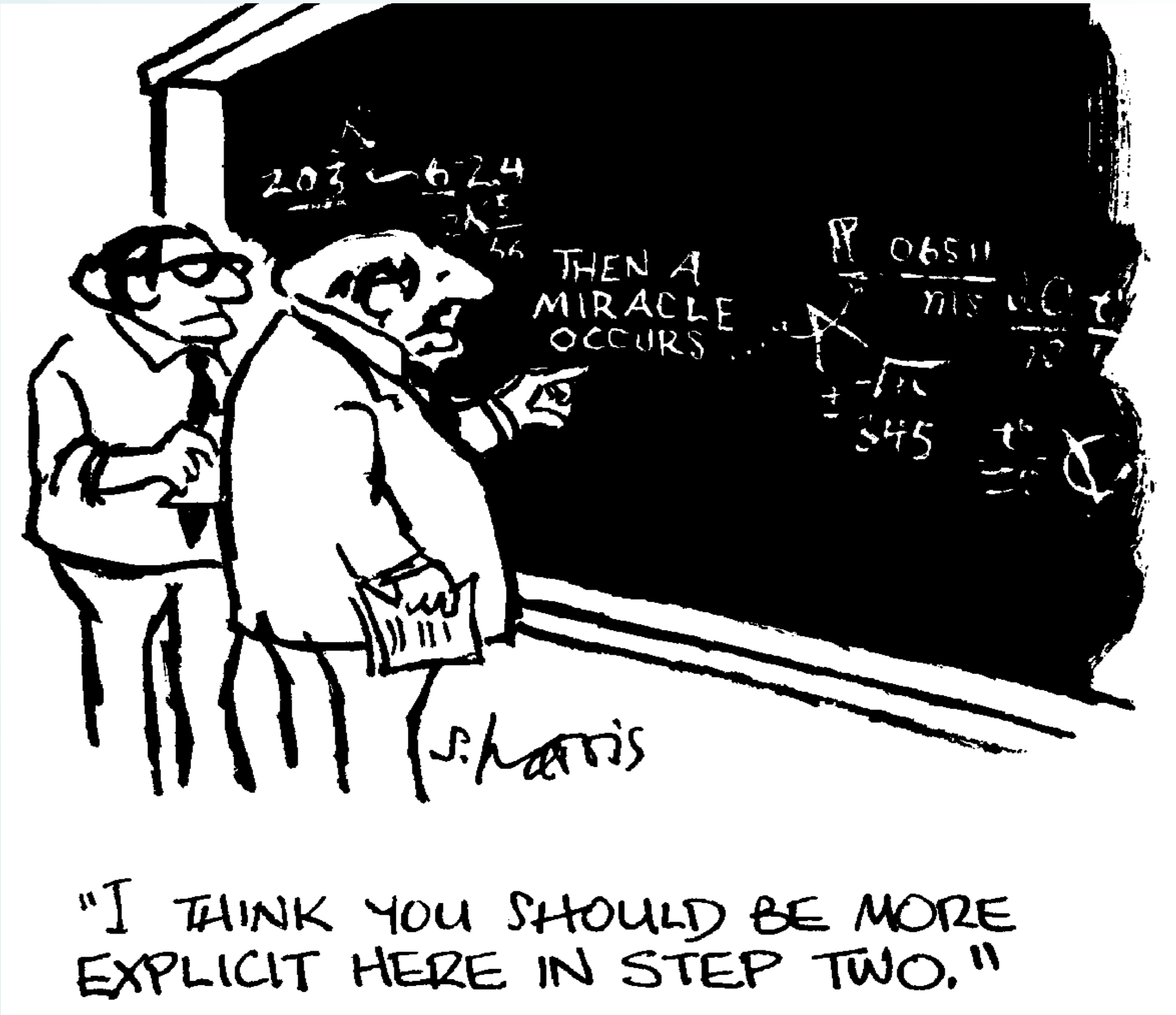
Figure 1: Dielectric wall induction accelerator configuration.





Conclusion

- Particle accelerators are an important and well established tool in medicine
- There has been considerable progress in recent years on the technical, biological and clinical knowledge
- Further research is warranted to fully exploit the advantages of charged particles with higher efficiancy and at lower costs



Thank you for your attention!

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